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RESEARCH ARTICLE

Tuberculosis I. The fight against tuberculosis has been mismanaged during seventy years, up till today. How did the mycobacterial community lose the war against TB?

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ABSTRACT

This review exposes the discovery of microbes by Leeuwenhoek in 1677, stresses the importance of food availability for the spread of tuberculosis, and underlines the absence of food security up till today for about 9.2% of the population, which favors the tuberculosis endemic. It describes the discovery of tuberculosis bacilli by Koch and the neglect by the physicians of plant drugs in favor of chemotherapy and surgery. The fight against tuberculosis was trusted by the World Health Organization in 1950, whose prime duty it was at that time to jugulate Tuberculosis. It was granted exemption of judicial pursuits to reach this goal. It immediately exploited this baffling privilege to abuse it and favor national commercial interests. The "Bacillle Calmette-Guérin" vaccine proposed by the French Ministry of Health in 1950 was known to be inadequately attenuated as early as 1927, was known by the World Health Organization to favor the spread of tuberculosis and nevertheless was promoted by the World Health Organization as a sole vaccine to combat the spread of tuberculosis. On the contrary, it reactivated dormant tuberculosis and leprosy cases and favored the endemic of both tuberculosis and leprosy. Despite this evidence, the vaccine was not removed but its deficiencies were steadfastly denied or else ignored. Alternative approaches, namely immunotherapy based on mycobacterium vaccae and a plant extract based on uleine, a substance known to stimulate the immune defenses of an organism infected by the tuberculosis pathogen, were combatted by the Belgian Ministry of Health and ignored by the World Health Organization. The chemotherapy was restricted during decennia to only four, plus streptomycin, which favored the rise of drug-resistant tuberculosis strains. New drugs proposed in addition to the four in use already, are expensive and riven by so many side effects, including death, that they are massively rejected by the patients. A blood test able to spot immune-depressed subjects and verify the efficacy of chemotherapy was banned by the World Health Organization and vigorously defamed by the Indian Ministry of Health. A review of the means used by the World Health Organization to fight the tuberculous endemy shows that these means are inadequate for the purpose, were so from the beginning of the fight, and were rarely to never amended in later times to become more efficacious.

Introduction

On October 13, 2016, L. Ditiu, Executive Secretary of the Stop TB Partnership (WHO), denounced the ongoing policy of eradication of tuberculosis that had shattered the lives of hundreds of thousands and had induced huge expenditures in vain during six decades. So dreary a chapter of errors, omissions, and crimes has been played out that we badly need policymakers who can face the risky reality they have created. Here is the 70-year-long sad story of the march toward fiasco. This story will undoubtedly bruise the ego of the actors who orchestrated the disaster. The magnitude of the problem currently posed by Tuberculosis demands an evaluation of the competence of the organisms and of the people in charge of the fight.

Background

Mycobacterium tuberculosis, the principal but not the sole causative agent of human tuberculosis, is considered the most successful pathogen that could infect (2 billion), induce (10.4 million), and kill (1.7 million) many people around the world. Besides this, the rapid evolution of Mycobacterium tuberculosis, from mono-drug-resistant to multiple drug-resistant [MDR-TB; isolates that are resistant to at least isoniazid (INH) and rifampicin (RIF)], extensively drug-resistant (XDR-TB; defined as MDR with additional resistance to both fluoroquinolones and at least one second–line injectable drug), and most recently extremely drug-resistant (XXDR) or totally drug-resistant strains (TDR-TB)], is threatening to make TB once again an untreatable disease.

Tuberculosis and leprosy plagued ancient Egypt and these diseases remained an object of concern throughout the world until World War II, after which public health agents of developed countries deemed these two problems solved. They were not but merely gone underground, to surge again with a vengeance. They are definitively linked to poor hygiene and poverty. The human health, from Antiquity down to the European Renaissance (circa Anno Dei (A.D.) 1500), was precarious because the quantity of available food was minimal. Upon the 8,000 generations of humans in their contemporary form, over 99.9% must have lived with a metabolism under tension because of a lack of food. The French Revolution was triggered by hunger: the population of Paris had no bread. Food scarcity and bread generate violence[2]. The agricultural production increased only from the middle of the 18th century on but still does not meet the needs. Last year, 30% of the world population was moderately or severely food insecure, i.e., 2.6 billion people. Millions of those went hungry. Today, in August 2023, 735 million people (9.2% of the population) are chronically hungry.

THE DISCOVERY OF MICROBES

Besides food penury, the principal alimentary risk was microbial, but this risk was ignored until A.D.1677.

Leeuwenhoek used a primitive microscope to observe microbes in 1677. These were extremely difficult to see prior to the advent of staining techniques, which were applied 200 years later, in the 1870s. Until the development of the achromatic microscope in 1830, microscope images were blurred by multi-colored images because light was not being brought to a common focus. (The erroneous early observation of a whole homunculus in the head of human sperm was the reason why the papacy forbade abortion from the moment of fecundation. Until that time, it allowed abortion before the" animation" of the fetus had taken place. It also erroneously indicated that woman plays only an ancillary role in the process of life generation). Once this technical barrier had been crossed, progress was rapid.

KOCH' PIONEER RESEARCH ON TB

On analyzing in 1880 the ideal conditions for culturing bacteria, Koch saw that the medium ought to be sterile, and transparent in order to show the area of growth more clearly and, above all, solid so that mixing of colonies of bacterial species could not occur. By sampling and re-inoculating a clean plate before the merging of different species of bacteria could occur, Koch obtained a pure culture of an organism. The Petri dish was devised by an assistant, Richard Petri, in1887.

Koch used the Ziehl-Neelsen stain in 1882 to observe under the microscope the presence of the tubercle bacillus in sputum smears. This is "bacilloscopy" and sputa are commonly said "smear-positive" or "smear –negative". The

bacilloscopy is a tedious process that demands the microscopist to observe one by one 100 microscopy fields and count the bacilli he sees in each field.

Sputum is not saliva and is hard to obtain from children and old people, who are thus difficult to diagnose for pulmonary TB by this method. Since the diagnosis of pulmonary TB is difficult to establish because the symptoms are inexplicit, the recognition of the positivity of sputum grants certainty and has become the cornerstone of the TB diagnosis that is deemed essential for the diagnosis. Bacilloscopy became a standard and obligated diagnostic because it lends certainty to the diagnosis.

This imperative does not consider the extra-pulmonary cases that make up about 30% of the cases, which thus escape diagnosis by this method.

Koch announced an additional standard diagnostic and a treatment, based on a TB extract named "Old Tuberculin". The second standard diagnostic, -the skin test (which is still abundantly used today)-, is the intradermal inoculation of a small quantity of tuberculin. Three days later, a swelling appears at the site of inoculation if the subject had been previously infected with tuberculosis. This is the Delayed-Type Hypersensitivity Reaction (DTHR). Using Old Tuberculin as a cure, Koch made a fortune before conceding that the Old Tuberculin awakened dormant tuberculosis (This awakening of dormant TB is an important phenomenon). The competition for a vaccine remained open.

ALLOPATHY VERSUS HERBALISTS

The laboratory-based germ theory promised cures for diseases through vaccines and drugs. In the absence of a state medical insurance system, the poor relied on "alternative" medicine, now regarded as unorthodox medicine. The fundamental difference between so-called "orthodox" and "unorthodox" medicine is that the former relies on restoring health through synthetic chemical drugs and surgery while the latter, exercised by herbalists, may use plant drugs. The germ theory rationalized allopathy by claiming that germs caused a patient's unease, and that health could be restored by the physician engaging in chemical warfare against specific "enemy agents". Allopathy triumphed through state registration of doctors.

The herbalists, in their immense majority women, were important members of their community and honored. Initially, women were barred from medical schools and women herbalists could not attend. The state registration of doctors changed radically their status. In the sixteenth century, they were seen as witches, with thousands of them burned alive. The physicians thus willfully organized the annihilation of herbal knowledge accumulated during centuries of patient observation and trial and error.

Although the allopathic doctors are scathing of herbalists and naturopaths, they were prepared to exploit "natural" methods when they were powerless to offer cures. Tuberculosis was the greatest killer in the 19th century and even if the cause was identified by Koch in 1881, no vaccine was found. In this situation, 19th and early 20th-century allopathic doctors were fully prepared to recommend naturopathic environmental remedies such as sending consumptive patients to the alpine peaks of Switzerland. It did not help these patients and doctors remained helpless until the discovery of streptomycin in 1940, although improved hygiene and food availability had by then greatly reduced in the West the rates of mortalities due to tuberculosis.

CHEMOTHERAPY

One consequence of the increased sophistication of organic chemistry in the 1880s was the chemist 's ability to synthesize new substances for use in industry, such as dyestuffs, and in pharmacology, as with the creation of "aspirin". Interest in the mechanism by which a dye is permanently "fixed" onto a colorless fabric led the German bacteriologist Paul Ehrlich (1854-1915) to speculate on the possibility of fixing a poisonous chemical onto target germs. This idea of "a magic bullet" -or chemotherapy- had its first success in 1911 when Ehrlich tested an arsenic compound on syphilitic patients. This drug was used on soldiers during World War I and on inmates who suffered from general paralysis which eventually overcame those suffering from tertiary syphilis. Ehrlich's "bullet" was ignored by bacteriologists for many years while they continued to try to fight disease with vaccine therapy. However, the German chemist Gerhard Domagk found a sulfanilamide in 1935 that

cured mice infected with bacteria, from which a complete range of other bactericides could be developed and manufactured, starting with penicillin. Streptomycin became available in 1944 and heralded the beginning of chemotherapy against tuberculosis.

THE CRIMINALLY CONDUCTED WAR ON TUBERCULOSIS.

The world thrives on deceit, greed, resentment, and stupidity. Janet Cornwall3 observed in 1997 that: *For the sake of return on investment and for the justification of huge public subventions and lavish expenditures on research and development, the management of the TB problem has chosen to ignore the reality of the situation and the urgency of solutions sensibly adapted to its needs*. And she adds: *"it is not knowledge which is lacking but the will to use it appropriately"*. This review supports her claim.

A. THE VALUE OF THE BCG VACCINE (BCG FOR BACILLE CALMETTE-GUÉRIN)

Considering that about 85% of the population of 172 countries is covered by BCG vaccination, that 3 billion doses of BCG have been prescribed in the last fifty years but that nevertheless a quarter to a third of the world population is infected by TB and that the number of cases is increasing throughout the world, one may not assert that the work performed over these last seventy years to combat it yielded satisfactory results. For decades, mycobacteriologists refused to admit that they had been misled.[1]

A vaccine based on the turtle mycobacterium M. chelonae developed by Friedman was used with satisfaction in France, Germany, and Italy in the thirties. After WWII, the French president General de Gaulle wanted to Make France Great Again. One of his endeavors to achieve this lofty goal concerned the Pasteur Institute where Calmette had developed in the 1920s a vaccine derived from a weakly pathogenic cow mycobacterium, M. bovis. Lignieres had shown in 1927 that this vaccine was poorly attenuated and had been shelved for this reason5. Nevertheless, de Gaulle ordered the BCG vaccine to be distributed throughout the French empire. De Gaulle succeeded in that by having the WHO assume the assignment. After World War II, the UNICEF (United Nations International Children's Emergency Fund) pushed by the French pediatrician Debré, chairman of its Subcommittee on Medical Projects and brother to the then French prime minister of President de Gaulle, donated 3 million dollars to the WHO to impose the BCG vaccination. The WHO accepted the bribe but discovered in 1948 that the BCG it analyzed in clinical trials in Finland and Denmark favored the spread of TB6. These adverse results were occulted, and the Friedman vaccine was mercilessly stamped out in France in 1950 in favour of the BCG vaccine.

The regression of the tuberculous endemy stopped slowly in France in 1987, followed with a 7% increase of TB cases in 1992 versus 1991. Pr. Grosset, Director of the national reference center for the surveillance of tuberculosis and atypical mycobacteria, mentioned 10,000 new cases in 19947 in France and concluded that the fight against TB was a total failure, implying (but not stating it, as he should have) that the BCG had been ineffective in stopping the progress of the disease. The BCG should have been abandoned at that moment, but Grosset said nothing, and the BCG continued its splendid career, as did Grosset's.

BCG CLINICAL TRIALS

1. The British Raj had not vaccinated the Indian population with the BCG. The Raj ended in 1947. The WHO/UNICEF provided support for a BCG vaccine Production Center at Guindy, Madras/Chennai, in 1948. Vaccination was extended to schools in almost all states of India in 1949. In 1950, Dr. P. V. Benjamin reported that tuberculosis infection was so widespread that no part of the country was free from it.

2. Indian villagers were vaccinated in 1950, who showed an excess of 90% TB cases[8]. To salvage the BCG, a committee appointed jointly by the Indian Council of Medical Research (ICMR) and the WHO acknowledged that the BCG was powerless against lung TB but that it provided substantial protection against childhood forms of TB such as tubercular meningitis and milliary TB; it recommended to give the vaccine before the end of the first year after birth. [Figure 5 (page 16) shows that BCG-vaccinated infants produce no protecting IgG antibodies against BCG].

3. That the BCG may induce tuberculous meningitis instead of preventing it was reported as early as 1928[4] and restated in 1988[9] but Grosset negated it in 1991[10]. The claim of

protection against TB meningitis was obviously a lie made to salvage the reputation of the ICMR and of the UNICEF/WHO and favor the further use of the BCG. BCG sometimes induces meningitis[9] and does not protect against tuberculous meningitis: a study performed in Tehran[11] on 100 children suffering from TB meningitis revealed that 30% of the 30 children with a history of vaccination died versus 28.6% among the non-vaccinated children. These percentages of mortality are similar. This result ruins the claimed efficacy of the BCG in tuberculous meningitis.

4. The promotion of leprosy by BCG was published in 1960[12] and again in the nineties[13,14]. A 9-fold excess of leprosy cases which affected only vaccinees less than 5 years old was observed in New Guinea during the first five years following BCG vaccination, but this promotion was not mentioned in the conclusion of the study[15].

5. The vaccination of 260,000 Indians in 1970 in Chennai (the Chingleput trial[16]) resulted after a year in a 100 % excess of symptomatic TB cases among the vaccinees. Four years after vaccination, the excess in symptomatic cases was 150 %. These excesses diminished in the following years, which allowed, by statistical manipulation, the conclusion that the vaccine was devoid of activity, not that it was iatrogenic, which it undoubtedly was.

6. Comstock followed the Chingleput trial. He observed in 1994[17] that former TB patients among vaccinees had a positive DTHR response, suggesting a reactivation of dormant cases. Swedish investigators confirmed this suggestion later, whose results I will expose infra[18].

7. The PNAS USA published in 1997 a study of the epidemic of TB occurring after the vaccination of an Amazonian tribe with BCG in 1994[19]. The authors concluded that the epidemic was due to immunological naivety. The authors who publish in the Proceedings of the National Academy of Sciences USA are not peer-reviewed. I indulge in a review here. This publication stated that the Brazilian health service observed the first case of TB among the Yanomami in 1965, with more cases appearing in the 1970s. The Brazilian Health Service vaccinated the Yanomami tribe in 1994 because tuberculosis cases were uncovered among its members. The tribe was thus exposed to TB before the vaccination took place and the TB patients present in its midst did not cause an epidemic. The result of the vaccination was that 82% of the vaccinated population contracted TB. The epidemiological proof that the origin of the epidemic was the vaccine is indisputable, but the authors of the study refused to admit this evidence.

8. The capacity of the BCG to favour infections by M. tuberculosis or reactivations of dormant infections was known by the Pasteur Institute, the French Ministry of Health, and the UNICEF/WHO since 1948 (clinical trials in Finland and Denmark). Comstock suspected it[17] and a Swedish study formally demonstrated it in evaluating the sensitivity to tuberculin (DTHR) of vaccinated and non-vaccinated children[18]. Three percent of the non-vaccinated controls were tuberculin-reactive versus 49% of the vaccinated children, a huge increase. The Swedish investigators attributed this elevated number not to the awakening of dormant infections by the vaccination, as they should have, but to the interference of the tuberculin with the BCG. However, they controlled the skin reactivity of their subjects also with avianin and scrofulascein, which would indicate infections with M. avium and M. scrofulasceum present in pet birds (canaries) and pet fishes, which Swedish children nurture during the long winter months. They found that 58% of the vaccinated children reacted to scrofulacein and 67% to avianin, while the frequencies found with these two sensitins in non-vaccinated children were only 25% for scrofulacein and 32% for avianin. The investigators concluded rightly that BCG favored infections by atypical mycobacteria but refused to extend this obvious conclusion to tuberculosis.

B. SOP AND DOTS

1. The Standard Operation Procedure (SOP) recommended isoniazid, rifampicin, ethambutol, and pyrazinamide (plus streptomycin) as the sole chemicals to use against TB. Streptomycin and rifampicin kill TB but also destroy the blood white cells involved in the immune defense system. The inclusion of these cytocidal drugs in a treatment was consistently shown to be beneficial, with treatment failure occurring in

only 5% to 10% of cases but rising sometimes to 44%[20].

How explain this? The tuberculous pathogen resides and multiplies in macrophages, i.e., white blood cells that are supposed to dispose of the pathogen via the synthesis of Nitric Oxide (NO), a potent molecule that can destroy it[21]. The pathogen succeeds in this by suppressing the production of nitric oxide by these cells. Clinicians administer the cytocidal drugs at their maximal tolerated concentration. These drugs may very well weaken the immune system of the patient to a point where his immune mechanisms become unable to dispose of the resident live intracellular mycobacteria subsisting after completion of the therapy or its early abandonment due to intolerance. Nowadays, the World Health Organization recommends the use of bedaquiline in the treatment of multidrug-resistant tuberculosis[22]. The drug is known to have severe side effects and to elicit mycobacterial drug resistance[23].

2. DOTS The Standard Operating Procedure (SOP) was completed with the concept of Directly Observed Therapy (DOT). Realizing that patients responded to a prolonged harsh treatment by strenuous attempts to escape it, a shorter treatment schedule was devised, hence DOTS for Short course. The method was successfully applied in American cities because the number of TB patients was relatively low, because these patients were largely cooperative, and because the strong political will to eradicate the disease was backed by almost unlimited funds. Elsewhere, this policy is unworkable24, due to costs, to crippling side effects (figure 1).

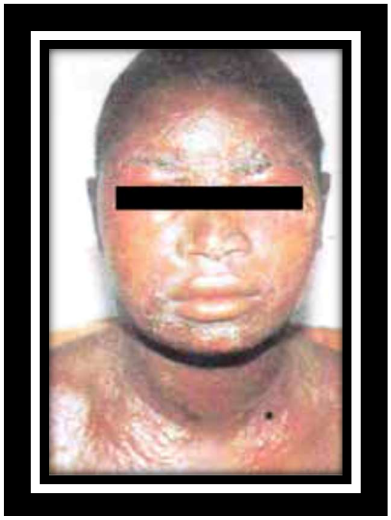


Figure 1. Cutaneous effect of streptomycin, isoniazid, and thiacetazone on an HIV-positive tuberculous woman observed 3 weeks after the beginning of the treatment (Clinical tuberculosis. Ed Davies, Chapman and Hall Medical 1994) and a difficulty in tracing patients who attempt to escape the too harsh treatment. The only way to handle these refractory patients was an immunotherapy and/or the boosting of their immune system.

C. M. VACCAE IMMUNE THERAPY

The essential contribution of immunotherapeutic agents would be to assist chemicals powerless in the suppression of an established immune-depressive infection. Several clinical trials of this new and esoteric treatment based on M. vaccae had persuaded its promoters that the treatment worked. The clinical trial made at Durban should have conclusively confirmed this. The clinical trial consisted of a single inoculation of M. vaccae at the beginning of the treatment of patients that were not chronic patients and of whom all the controls not receiving the immune therapy survived. The patients selected for inclusion in the Durban trial were not sorted out according to the intense degree of their immuno-depression (easily monitored by a blood test). Besides, the clinicians in charge of the trial followed the Helsinki recommendation that the control subjects of clinical trials must receive the best treatment available, and the chemotherapy alone was sufficient by itself to improve the health of the controls. Under these conditions, the immediate effect of the immunotherapy was so limited that M. vaccae immunotherapy was claimed, mistakenly, useless[25]. When the agent was used repeatedly, i.e., injected intramuscularly monthly for 6 months to chronic patients resistant to isoniazid, streptomycin, and rifampin, 9 of 24 cases were cured after 18 months follow up, versus 1 of 24 cases in the control group[26].

D. ULEINE/ PARA PAO ASPIDO.

The first line of defence against an invading pathogen is the production of highly reactive nitric oxide by macrophages and other cells. The antimicrobial properties of Nitric Oxide (NO) are well established since 1995. NO is active in vivo against mycobacteria. I developed a food supplement - Pao aspido distributed by Parabolic biologicals- that stimulates the

synthesis of Nitric Oxide27. It was proposed to Stop TB in 201428 and it was promptly removed.

Here, is a small parenthesis: I submitted a manuscript entitled "Preventive food complements and preventive TB diagnostic" to the Journal of Preventive, Diagnostic and Treatment Strategies in Medicine | Published by Wolters Kluwer – Medknow [2]. In this manuscript, I described the stimulating effect bread, now consumed practically worldwide and especially by African populations, had on the aggressive behavior of the populations abundantly consuming it. I also pointed out the benefit of taking a food supplement based on uleine (in this case, Pao aspido) to protect oneself against pathological aggressions of external (viruses as the corona virus and HIV[29], and bacteria, including tuberculosis) and internal (cancers) origin. To my surprise, I discovered that the editor of the journal (Parisa Farnia) had redacted the article. She changed the text in figure 2 and replaced the word "wheat" by "corn". Columbus discovered America in 1492. Corn is a New World product that was widely neither known nor grown in Europe when Breughel painted the harvest of wheat in 1565.

The food supplement "Para Pau aspido" is based on uleine, which stimulates the production of nitric oxide (NO). Nitric oxide kills the tubercle bacillus that has however the particularity to multiply in the very macrophages that synthesize the NO! In other words, the pathogen shuts down the production of NO by the macrophages it invades, and uleine restores this production. This supplement was included among the Belgian authorized food complements (list 3) and was obviously of immense interest. On June 13 2007, a ministerial edict promulgated by the Belgian minister of health Rudi Demotte moved this food supplement from the list of authorized foods (list 3) to the list of forbidden foods on the ground that this food supplement was botanically speaking not well characterized and was toxic, mutagenic and teratogenic, although it had been proven without any doubt well before that time to induce none of that, to be well characterized and be innocuous27. Why is this important? Because the preparation and sale of the food complement Pao aspido was forbidden not only in Belgium but throughout the whole world. Demotte shamelessly and blatantly lied and deprived the whole world of an excellent way to help the organism fight bacteria and virus aggressions (including TB and the Coronavirus), as well as some cancers. The shameful ministerial edict that enforced the ban was never abrogated and is still in force (figure 2).

Figure 2. Infamous Belgian ministerial edict displacing on false motives the food supplement Aspidosperma from list 3 to list 1.

PROGNOSIS

As I explained, pneumologists are obsessed with certainty, which they gain by the detection of the pathogen in sputum. The WHO recommends various antigen-detection tests (sputum smears, Xpert MTB/RIF[30], line probe assay, and liquid cultures) for diagnosis and accepts a costly interferon-gamma release assay for the detection of latent infections[31]. Antibodies against TB are produced in latent infections because the pathogen has at the beginning of an infection, not suppressed the immune capacities of the host. Infected subjects produce a range of answers stretching from vigorous amounts of antibodies produced at the beginning of the infection, to weak and even zero production after the pathogen has succeeded in suppressing the immune capacities of the host (Figure 3).

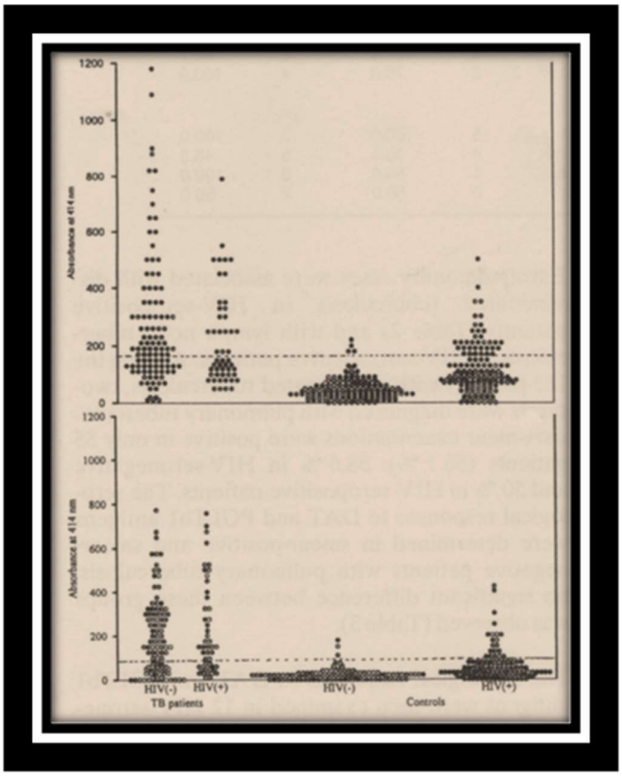


Figure 3: Levels of IgG antibodies directed against diacyl trehalose (a) and glycolipid (b).

Diacyl trehalose (a) and glycolipid (b) were supposed associated with active disease and thus showed no negative results in the case of smear-positive samples. The results shown in this graph are identical to those in the blood test developed by Sarman Singh[32] and me, who used other antigens.

The Anda TB serological test was available since 1989 and Wirmann showed it useful for the detection of latent mild infections in exposed groups in 1989[33] and Kaustova among some cancer patients in 1995[34]. A routine serological monitoring of exposed groups is not anymore possible because the WHO banned serological tests in 2011[35] on the ground that they are inaccurate.

Grosset and Mauch vehemently rejected the test. I submitted a manuscript in French to an editor who had the manuscript evaluated (peer review) by Jacques Grosset, who was in those years responsible for the fight against TB in France. A reviewer is supposed to help the author produce a manuscript that is exempt from gross errors in the design or interpretation of the results, which is what the editor wants. Here is his evaluation (figure 4): he did not help at all but notes that antibodies were detected among patients suffering from lung cancer, which he claimed were "false positive". He failed to recognize that they were genuinely suffering from a mycobacterial infection[34]. He said that they "mimic" (simuler) tuberculosis. The conclusion ("this work is not original and has no interest") severely questions his honesty and intelligence which must both be much less acute than he and the editor assume them to be. This blind reliance of the editor on the honesty, superior intelligence, and knowledge of a reviewer who is so obviously in a severe shortage of all three of them is scholasticism, an attitude that I will develop more at length *infra*.

I give in addition the evaluation of Mauch (figure 5), who had spent many years on the development of a blood test for TB and failed. As is clear from his objections to my work, Mauch used himself as negative controls patients who were genuinely infected by TB (pulmonary tumors) and thus had antibodies against TB. This inclusion of positive cases among controls led him to the false conclusion that all TB serology, including mine, must suffer from a lack of specificity. Both opinion leaders were insulting me.

https://drive.google.com/file/d/1qK0Fe23mKzaZsKl7TAXVrb6yqrTFl71i/view?usp=sharing

Fig. 4. Peer review by Grosset of a manuscript describing the usefulness of a blood test for tuberculosis.

https://drive.google.com/file/d/1PKNhiG-Js7XMmywL4mcaS1CE8KgsDOMO/view?usp=sharing

Figure 5. Peer review by Mauch of a manuscript describing the benefits of use of a blood test for TB antibodies.e.

THE HERD MEDICINE APPROACH

The accepted paradigm that governed for many decades the war against tuberculosis held that TB is in regression, that the BCG vaccine and 4 drugs (plus streptomycin) are sufficient to stop the spread of the disease and heal the patients. The resounding failure of this policy led to the use of other drugs in addition to these four: in March 2018, the TB action group (TAG) increased the number of drugs for drug-resistant TB cases. Prof. Grosset recommended them.

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens.

Group A: Include all three medicines (unless they cannot be used) Levofloxacin OR Moxifloxacin (Lfx Mfx) Bedaquiline (Bdq) Linezolid (Lzd)
Group B: Add both medicines (unless they cannot be used) Clofazimine (Cfz) Cycloserine OR Terizidone (Cs Trd)
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used Ethambutol (E) Delamanid (Dlm) Pyrazinamide (Z) Imipenem-cilastatin OR Meropenem (Ipm-Cln Mpm) Amikacin (OR Streptomycin) (Am (S)) Ethionamide OR Prothionamide (Eto Pto) p-amino salicylic acid (PAS).

This table is confusing, these chemicals are expensive and produce so severe side-effects (vomiting, liver damage, eye damage, and sometimes death) and demand so many controls

during monthly follow-ups that it is not feasible nor realistic to apply them in those countries that need them most. The patient promptly abandons their intake as soon as recovery is noticed. Chatterjee pointed out[36] that Grosset was intellectually too poorly equipped to conduct fruitfully clinical trials on mycobacteria, which he conducted[37] against common sense.

7 DECADES-LONG INERTIA

The evidence is that, as late as 2023, the problem of TB remains handled with the concepts that were in force during the 20th century. It is a herd medicine approach: find the bug with newly developed sophisticated instruments (The Xpert MTB/RIF diagnostic tool), stamp it out with powerful new drugs (bedaquiline and others) given at their maximal tolerated concentration and protect the population with the BCG vaccine. Prevention is totally ignored.[38]

New sophisticated antigen detection methods (e.g., the Expert/RIF antigen test, which Singh has shown to suffer from severe deficiencies[39]) are nothing more than gimmicks that consolidate the old 19th-century concept: molecular tools build a technical scaffold in front of a facade that stands alone, without the building that it is supposed to clad. The technical skills involved in these methods help hide the poverty of the results obtained. These huge healthcare expenditures reflect huge corporate profits rather than human needs and the gap between these expenses and promises and performance makes manifest our vulnerability to propaganda[40].

In view of the 7 decades-long inertia, on Wed, Nov 29, 2017, I asked the Treatment action group Tuberculosis (TAG) what had been done, -and not done-, to achieve the current tuberculosis disaster: TB blood tests revisited":

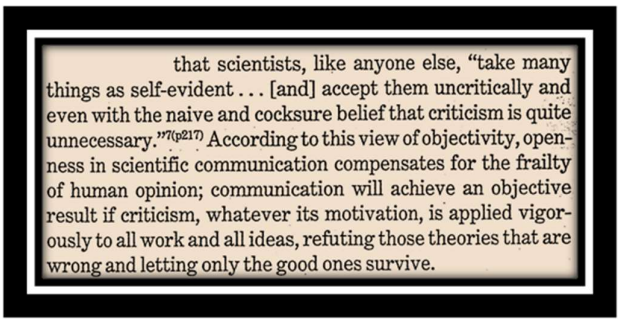
https://drive.google.com/file/d/1TBsar_CdEUZSm68KeVz5ptlughM47GL9/view?usp=sharing

In fact, I merely asked in 2023 the question asked by Cornwall in 1997, 26 years previously. Edward A. Nardell, mycobacteriologist[20] and Professor of Medicine at Harvard Medical School choked and answered (I reproduce his answer in extenso) that: "*There is much in the highly inflammatory and accusatory posting by Maes on Nov 29, 2017, to indicate bias and self-serving motivation - requiring that this forum, and others like it, should be moderated. I was pleased to hear from the organizers of plans to do just that. There is no role for this kind of diatribe in scientific discourse.*

This is an unfortunate and heavily biased argument. When WHO acts it does so based on evidence and under the advice of the most knowledgeable experts in the world. This diatribe appears to be self-serving and not evidence-based. Please remove me from this mailing list.

According to Nardell, attempting to improve the lot of desperate TB and leprosy patients who lurch from one crippling treatment to the next in hopes that something changes the fate of a fight racing toward doom is condemnable and self-serving, and "there is no role for this kind of diatribe in scientific discourse". That I express my concern vigorously without resorting to euphemisms is another reproach, but each author has his own style and I believe that one does not oppose an asinine behavior while leaving the ignorant unscathed.

Nardell unashamedly advocates censorship for criticism. This plea is shocking coming from a scientist. Popper wrote in "The Open Society and its Enemies", Princeton U. Press, 1966:


that scientists, like anyone else, "take many things as self-evident . . . [and] accept them uncritically and even with the naive and cocksure belief that criticism is quite unnecessary."[7(p217)] According to this view of objectivity, openness in scientific communication compensates for the frailty of human opinion; communication will achieve an objective result if criticism, whatever its motivation, is applied vigorously to all work and all ideas, refuting those theories that are wrong and letting only the good ones survive.

Reviewers and journal editors repeatedly and consistently disdain Popper's advice and put submitted manuscripts to review by "peers", but they are not peers but usually opinion leaders who have strong opinions, which they teach unwaveringly sometimes during decennia. This behavior of the editors is based on the acceptance of professorial authority, which is scholasticism. Robert May wrote in 2001:" The world that deferred to authority (scholasticism), advised by confidential cabals, has gone. Consult widely and get the best people, but also make sure dissenting voices are heard; and above all, be open and publish all advice". This eminent

scholar evidently ignored the reality of the TB situation. The world advised by confidential cabals is still very much present as per the following example. M. Pai prides himself of being an expert on TB. He counseled the Indian Ministry of Health to apply the Revised National Tuberculosis Program (RNTP) (fig. 8 page 18) that generated a flurry of new cases of TB in India: on February 11, 2013, the British Medical Journal announced: Tuberculosis looks set to defy concerted efforts to treat it successfully with powerful drugs, turning the clock back to the 1930s". On February 20, 2013, The Wall Street Journal added: "India's new strategy actually makes disease more drug resistant, doctors say". On January 9, 2014, a post on the LinkedIn group "Healthcare India" warned of corruption: "there is a huge possibility of medication or diagnostics being advised disproportionate to the need, and people at large feel that is what is happening". Nevertheless, Pai's reputation remained unscathed when he confided to the Bill and Melinda Foundation that all, absolutely all of what I said was false: contrary to what I claim, the BCG works superbly, the drugs are very efficacious, the Indian RNTP is in good hands and on its rails and, trust me, TB will soon be vanquished. Not everybody believed him.[40] "The Lost War Against Tuberculosis 14 February 2018" covers the subject in 19 pages. https://drive.google.com/file/d/1jogOkVTrLtcwNAsShiVQ_JLAtZXfeTdP/view?usp=sharing

Nardell praises the WHO. He feigns to ignore the TV station ARTE that diffused on April 4th of the year 2016: "*The WHO in the claws of lobbyists?*"

This documentary denounced the corruption of the WHO officers, their acceptance of subventions from pharmaceutical industries and private organizations, and the coercion exercised on the Organization by powerful States that impose their own interests to the detriment of patients. The documentary devoted 6 minutes to TB. It started with the reproach that the industry did not develop new drugs against TB during these last 50 years because these were not profitable. This is a lie. The industry stopped developing drugs as soon as the WHO restricted, during 7 decennia, the number of drugs to four plus streptomycin.

It continued with Mario Raviglione, in charge of the TB department at the WHO, who affirmed the interest of the WHO for poor countries. He did not mention that its interest in India, concretized in the implementation of the RNTCP (Revised National Tuberculosis Control Program) applied in 2012, resulted in a considerable progress of the spread of the disease in that country, instead of a regress.

Raviglione pursued by chanting the merits of the newly introduced Bedaquiline, undisturbed by the significant excess deaths this drug generates among TB patients, nor did he see any problem with the gift to the WHO of 40 million dollars by Johnson and Johnson, the purveyor of Bedaquiline. The drug has merits but must be administered cautiously under attentive direct medical supervision solely to MDR-TB cases and is thus restricted to developed countries. He claimed he never heard of drug resistance to Bedaquiline although this resistance is well documented.[41] Raviglione stated that the critics of the drug do not know what they are talking about.

The WHO banned blood tests for TB knowing that the ban was illegitimate, based on statistics that did not allow such a decision.[42] Blood tests are vital for diagnosis in rural areas.[43] This devious rejection does not sustain the claim by Nardell that: "When WHO acts it does so based on evidence and under the advice of the most knowledgeable experts in the world". They are on the contrary ignorant and corrupt.

Conclusion

The oversimplification of a complex problem is not unusual among scientists. *Oversimplification one: The BCG vaccine*

Of the 1.2 million infants born each year worldwide, approximately 88% receive a BCG vaccination. The vaccine fails to induce the production of IgG antibodies (Figure 6).

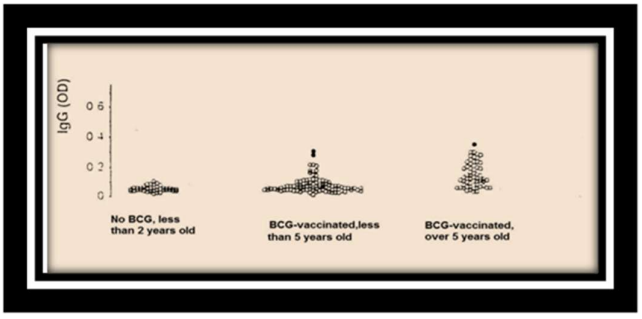


Figure 6. No production of IgG antibodies in the non-vaccinated group, as is expected, but antibodies in the two vaccinated groups are also absent, with respectively two very weakly positive cases and one case barely emerging above the cut-off line. These borderline-positive cases may be traced to increased exposure of the children to contacts outside the home (i.e., nursery, kindergarten, and relatives).

The vaccine currently covers about 80% of the world population. Lignieres showed as early as 1928 that this vaccine was not fully attenuated, rarely elicited a skin test reaction[44] and gave occasionally TB infections instead of protecting against them. Since the vaccine does not routinely produce a skin test reaction while the Pasteur Institute led the clinicians to believe it does, the vaccine is re-inoculated until a true but cryptic tuberculous infection betrayed by a positive skin test has been achieved. (The study performed in Sweden on vaccinated and non-vaccinated children mentioned *supra* is clear proof of this). The moral authority of the Pasteur Institute and of WHO, and the trust they inspire, prevent a sound assessment of the value of this vaccine, with the consequence that the fight against TB is compromised by the near-universal promotion of its spread (as well as leprosy [12,13,14,15]) via the BCG vaccination.

OVERSIMPLIFICATION TWO: THE IMMUNOSUPPRESSIVE ACTIVITY OF THE TB PATHOGEN.

On page 189 of the textbook Tuberculosis, a comprehensive clinical reference, published in 2009 by Saunders[45], the authors Dick Menzies, Kevin Schwartzman and Madhukar Pai wrote: The sensitivity of serological assays which target mycobacterial antigens putatively associated with active TB should be highest among persons with smear-positive pulmonary disease – because of the high bacillary load and ensuing stimulation of antibody production. This statement says the contrary of the reality. On the contrary, a heavy load associates with absence of antibodies because the immune-suppressing activity of the pathogen is then maximal. This baffling negation of the immune-depressing activity of the pathogen, known since 1996[46], and still expressed in this textbook in 2009, leaves one disarmed and desperate. These authors must know that they are saying what is not. They willfully mislead their readers.

On the other hand, an immense majority of mycobacteriologists still believes that the pathogen does not elicit the synthesis of antibodies at all and that all immunological protections are traced to the cellular immunity evidenced by a skin test.

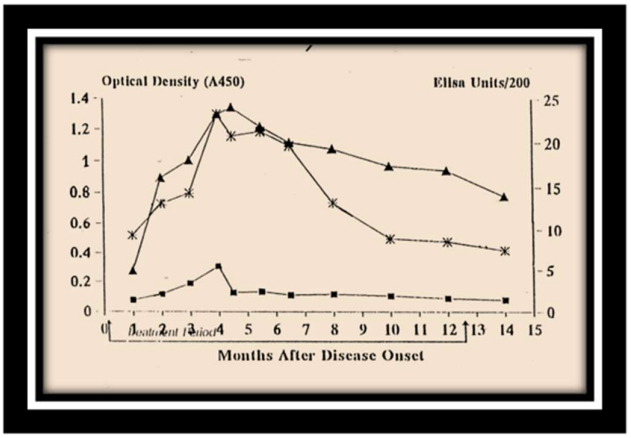


Figure 7. IgG (*), IgM (■) and IgA (▲) production during treatment of a patient for 12.5 months. The bacillus had supressed the production of IgM (■) and IgA (▲) but IgG antibodies (*) were still detectable at a low level, at entry. The treatment was beneficial and spurred the synthesis of IgA and IgG antibodies.

I have battled during three decennia to have my mycobacteriologists' colleagues admit that tuberculosis is immunosuppressive, that antibodies are produced at the beginning of infection but often not detected or detected at a low level later because the pathogen inhibits their production, and that serological monitoring of the disease would be a useful adjunct to prognosis and treatment in that the immune-depressed patients would be recognized and their immune reactivity boosted by successful chemotherapy as well as by the absorption of a food supplement rich in uleine known to be useful in the prevention and treatment of infectious diseases, and available. (Note that Nardell, like so many allopathic physicians, scorns herbal medicine and never tried this food supplement out). My efforts remain up till today, without success. Worse, the WHO advised a ban on serology in 2011, based on obviously inadequate statistics and a crass ignorance of the immunopathology of TB. India blindly endorsed the ban in 2012 (figure 8).

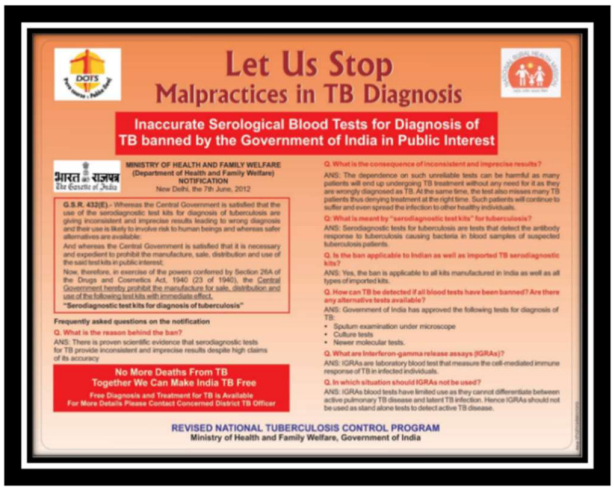


FIGURE 8. Indian ban of blood tests. No more deaths from TB. Together we can make India TB free (June 2012). M. Pai advised the ban, to replace serology with an expensive antigen-detecting test. We are now in 2023 and the number of deaths has not diminished.

The ban was supposed to leave the place for the newly developed expensive molecular antigen-detecting test, the Xpert MTB/RIF diagnostic, as explained in the fourth question. The claimed inconsistent results expressed in question one are by no means inconsistent but reflect the intensity of the abrogation of the immune response inflicted by the pathogen. This precious information should interest any clinician. The meta-analysis and the WHO experts' analysis that led to the ban of serological tests were performed with the greatest mathematical frenzy but ill-analyzed by statistical ineptness and ignorance of the immune-inhibitory capacities of the pathogen. It also frivolously ignored the basic requirements of a seriously conducted analysis. The war against TB requires better leaders.

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