ON LEPROSY AND TUBERCULOSIS SEEN AS DISEASES DEVELOPING FROM METABOLIC CAUSES

Resumen de dos conferencias pronunciadas
por el Académico Correspondiente Dr. Meny Bergel
en la Academia Nacional de Ciencias de Buenos Aires
en junio de 2011

ON LEPROSY AND TUBERCULOSIS SEEN AS DISEASES DEVELOPING FROM METABOLIC CAUSES[1]

A comprehensive summary of two conferences

I. THE METABOLIC THEORY OF LEPROSY

II. THE ROLE OF ANTIOXIDANTS ON THE SETTLEMENT AND DEVELOPMENT OF TUBERCULOSIS

Dr. MENY BERGEL

Resumen

Este trabajo tiene el doble objetivo de reivindicar primeramente el origen de una tesis relacionada con la causalidad y desarrollo de la lepra en individuos. Fue formulada por primera vez en 1947 y, desde su enunciado, ha sido confirmada recientemente por trabajos de laboratorio y de campo y por la creciente evidencia resultante a partir del conocimiento de los efectos del estrés oxidativo. Luego, dicha hipótesis devino una teoría, denominada Teoría Metabólica de la Lepra (MTL), que explica por qué y cómo se desarrolla la lepra en humanos, a la par del rol del bacilo M. leprae. En segundo término se reivindica un conjunto de trabajos que siguieron sobre el rol del metabolismo, a través del estrés oxidativo, en el contagio y desarrollo de la tuberculosis, que fue desarrollado casi simultáneamente (1950) con la hipótesis mencionada y la MTL. Estudios muy recientes verifican lo acertado de la propuesta original. Una vez más, se podría haber utilizado una aproximación diferente al estudio y tratamiento de dicha enfermedad que, probablemente, hubiese beneficiado la salud global de la población.

[1] This paper has been edited and revised by Acad. Juan Carlos Ferreri, National Academy of Sciences at Buenos Aires and Acad. Alberto Boveris, National Academy of Pharmacy and Biochemistry, Buenos Aires, Argentina. In the opinion of both editors, this communication may confirm an early, original Argentinean contribution to a contemporary scientific hypothesis.

Abstract

This paper has a double objective. It is firstly aimed at vindicating the origin of a hypothesis related to the causality and development of leprosy in human individuals. It was firstly formulated in 1947 and, since its enunciation, it has been confirmed by recent laboratory and field studies and growing evidences coming from the knowledge in oxidative stress effects. The hypothesis became a theory, denominated Metabolic Theory of Leprosy (MTL), which explains why and how leprosy develops in humans and which is the role of the M.leprae bacillus. Secondly, a pioneering study (and its sequel) on the role of metabolism via the oxidative stress in the settlement and development of tuberculosis is also vindicated. This study was developed quasi simultaneously (1950) with the above mentioned thesis and the MTL. Quite recent studies have verified the correctness of the original proposal. Once again, a different approach to the study and treatment of an illness could have been applied, in this case to tuberculosis which, perhaps, would have benefited the health of the global population.

I. THE METABOLIC THEORY OF LEPROSY

Introduction

In a very brief overview, the Metabolic Theory of Leprosy (MTL), see references of previous works by the author (Appendix I), consists in considering this disease as a process occurring in humans with certain genetic profile, who develop a metabolic auto-oxidative process that enables colonization by Hansen bacillus (M. leprae). If this chain of causal events is not fulfilled up to the point of the arrival of M. leprae, the disease will not occur.

This chain process may be described as: Organism → Genetic impairment → Auto-oxidative metabolic process (oxidative stress) → Colonization by M. leprae → Leprosy.

The process implies that M. leprae only participates in the final stage of a series of events which, if not present, prevent the occurrence of leprosy. This reasoning provides an answer to two possible main questions: a) is leprosy a metabolic disease of genetic origin with a final addition of an organism? or; b) is it an infectious disease caused, as necessary and sufficient requirement, by M. leprae? In the framework of MTL, the last question is not appropriate or relevant.

In order to introduce the MTL, some essential features of leprosy as a disease must be known. It was firstly thought that leprosy was

a hereditary disease or an illness caused by environmental or miasmatic factors or by the intake of inadequate foods, like dried, salted and fermented fish. In this state of art, the end of XIX century was reached, when bacteriology burst into the field of medicine. Pasteur was its most distinguished representative. Later, microbes were discovered as causative agents of diseases and in 1873 Hansen discovered the homonymous bacillus, followed by Neisser in 1880, who found the bacillus in lepers' lesions. Then it was natural to attribute the cause of leprosy to M. leprae. In that time, a few microorganism-caused processes had been described, as some fungal illnesses, carbuncle and tuberculosis, the last one in 1882. Then, several discoveries occurred, as the etiology of typhoid fever, cholera, tetanus, gonorrhea. In our view, when Hansen bacillus was discovered in lesions of lepers, the assimilation of the concept of presence of M. leprae to the concept of illness was erroneous, but not unexpected. This mistaken interpretation of Hansen's discovery does not impair its paramount importance.

Following the finding of Hansen bacillus, according to the concepts of the time, the infectious etiology of leprosy was established. Consequently, the tenets for infectious diseases were applied to this illness. Hansen himself tried to inoculate his bacillus into the cornea of a patient, which caused a legal prosecution. Also, trials with this pathogen were started: inoculation to laboratory animals, cultures in test tubes and experiments with vaccines.

As expected, from a therapeutic perspective, every antibiotic and chemotherapeutic agent at hand was tried in order to "kill" Hansen bacilli and sterilize lepers like Ehrlich's "terapia sterilisans magna". From another point of view, healthcare measures indicated by the infectious disease condition were implemented, as isolation, hospitalization for treatment in leprosariums or leproseries, repressive laws, marriage ban, mandatory treatment of household members and relatives and preventive treatment of children, that is, when leprosy was labeled as an "infectious disease", with "high risk" and "high infectivity", the whole mentioned operation was launched.

In what follows, the actions of leprologists, their consequences and lessons learned from attempts to discern the peculiarities of leprosy will be summarized:

a) The search of an inoculation chancre, which was not found and is no longer considered. Regarding the incubation period, fantasies flew high and periods from to 3 to 5 years and up to a maximum of 20 to 30 years were mentioned. Everything

was conjectural because this said period was never conclusively established.

b) Conjugal leprosy and infection were also unresolved topics, as contagion was never determined and conjugal leprosy was discarded by throughout statistical studies.
c) Leprosy prevention; preventoria were intended to preventing leprosy "endemics" and had their peak in the middle of last century, but have now disappeared.
d) Isolation is no longer practised anywhere in the world, because if conjugal leprosy does not exist, isolation does not make sense.
e) Regarding vaccination, either with Hansen bacterial antigens or with BCG alone or associated to other mycobacteria has so far given negative results.
f) A positive side effect comes from the inoculation of Hansen bacillus to the armadillo or some monkeys that still stands. This was useful for producing grams of bacilli that were used for preparing the above mentioned vaccines, whose usefulness has not been yet demonstrated.

In summary, the bacteriological approach to leprosy did not provide essential information to clarify the etiology and pathogenesis of the disease.

Let us consider now the therapeutic aspect of leprosy, as related to the infectious conception of the disease. All the known antibiotics have been tried in the treatment of leprosy and all of them failed. As a paradigmatic example we will mention the case of rifampicin. This antibiotic, with a powerful bactericidal activity against Hansen bacillus, was administered initially at high daily doses. Then dose levels and dosing were reduced and now it is recommended to administer it once monthly. This came upon the recommendation of the World Health Organization (WHO). It is worth mentioning a quote from Rees (1): "If rifampicin does not cure leprosy, no other antibiotic will do so, given its extraordinary activity against Hansen bacillus, its low toxicity and excellent absorption and metabolism".

At present, lepers are treated with dapsone, an industrial antioxidant with multiple metabolic activities, which is not used against any other infectious disease but is used in several metabolic diseases. A small monthly dose of rifampicin and clofazimine, a chemotherapy agent that is not used in monotherapy against leprosy, is added to dapsone. However, monotherapy with dapsone is common and has

been the single effective treatment of leprosy for decades and is at present an excellent treatment for this disease.

In summary, leprosy did not respond to its labeling as infectous disease. This must have happened because it is not an infectious disease, but a metabolic one. Even though Hansen bacillus is present in all lepers, its presence is not a synonym of cause, i.e. the bacillus is present in lepers but is not the cause of leprosy. Moreover, the Hansen bacillus is found in normal subjects of the endemic areas. Therefore: leprosy is neither an infectious disease nor a contagious disease; it is not acquired through intimate and prolonged contact with other patients; it is not prevented with vaccines and can not be treated with antibiotics.

Clinical evidences on the role of metabolic diseases on leprosy development in humans

B. R. Chatterjee (1992) considered the Bergel hypothesis in a search for its possible justification and with a critical approach. In this sense, Chatterjee considered the leading idea of the MTL, and concluded that although non disputable evidences were found that could substantiate MTL as a fully standing theory, the administration of dapsone was nevertheless recognized as producing clear results and playing an essential role. Chatterjee attempted to explain its role as to "add substance and lend credence" to MTL. Also, his analysis led him to conclude that "Only by running a controlled trial of low-dose dapsone monotherapy may provide more conclusive evidence on the correctness of Bergels' theory". Unfortunately, he did not have too much hope at that time that said trial could be undertaken because of the way in which multidrug were administered as part of official therapy of the WHO program.

Bergel formalized his hypothesis as a theory, denominated "Metabolic Theory of Leprosy" in 1988, but it remained considered as a hypothesis. In the last decade, 11 experimental works have been published (1-11) in agreement with the view that the MTL may fully stand. These studies put into its real perspective the role of metabolism in the development of leprosy in humans. To summarize, a *vis a vis* comparison of the infection theory and the MTL is provided in tabular form in Table 1.

In what follows, the main conclusions of the aforementioned studies are summarized along with some argumentation. When ap-

propriate, some excerpts are included. In this context, the concept of oxidative stress was introduced by Sies in 1985, as a situation in which an unbalance occurs between the level of oxidants and the level of antioxidants, resulting in biological damage. The concept has been fully accepted and is currently used for cells, tissues and whole organisms, as cellular and systemic oxidative stress.

Vijayaraghavan et al. (3) states that tissue disruption in leprosy comes mainly from the effects of free radicals, with malnutrition playing an essential role. In their studies they noted "a significant lowering of the antioxidant status, both enzymatic and non-enzymatic antioxidants, in paucibacillary and multibacillary type of leprosy cases, with an increase in the level of lipid peroxidation products as expressed by thiobarbituric acid reactive substances". They also concluded that when patients were co-administered vitamin E and other lipid soluble antioxidant with multidrug therapy, the overall protection against the oxidative stress remediated damage during the chronic disease stage. In the same trend, Lima et al. (4) concluded that "the evaluation of oxidant/antioxidant status in these patients can be an important factor in the treatment, control, and prognosis of this disease". Bhadwat and Borade (5) measured the biochemical marker of lipid peroxidation, malondialdehyde (MDA), in the plasma of 70 leprosy patients. Erythrocyte superoxide dismutase activity (SOD) was also measured in the patients. The results strongly indicated increased oxidative stress in lepromatous leprosy, which appears to have resulted from low antioxidant defense. Vijayaraghavan et al. (6) studied the antioxidant status of leprosy patients who were under multiple drug therapy and those who, at the same time, were co-administered with vitamin E. These authors concluded "that exogenous supplementation of the antioxidant vitamin E certainly favors the leprosy patients in protection against the oxidative stress and free radical-driven damage during the chronic course of the disease and antileprosy chemotherapy". Then the essential role of antioxidant status was again confirmed in the treatment of leprosy. Other researchers reported similar findings (7-10), which are fully consistent with the previously referred role of antioxidants in relation with the development of leprosy. The recent work by Cruz et al. (11) has particular importance to support the MTL. It is fair to excerpt their abstract, stating that "Intracellular pathogens survive by evading the host immune system and accessing host metabolic pathways to obtain nutrients for their growth. *Mycobacterium leprae,* the causative agent of leprosy, is thought to be the Mycobacterium

most dependent on host metabolic pathways, including host-derived lipids. Although fatty acids and phospholipids accumulate in the lesions of individuals with the lepromatous (also known as disseminated) form of human leprosy (L-lep), the origin and significance of these lipids remains unclear. Here we show that in human L-lep lesions, there was a preferential expression of host lipid metabolism genes, including a group of phospholipases, and that these genes were virtually absent from the mycobacterial genome. Host-derived oxidized phospholipids were detected in macrophages within L-lep lesions, and one specific oxidized phospholipid, 1-palmitoyl-2-(5,6-epoxyisoprostane E2-sn-glycero-3-phosphorylcholine (PEIPC), accumulated in macrophages infected with live mycobacterium. Mycobacterial infection and host-derived oxidized phospholipids both inhibited innate immune responses, and this inhibition was reversed by the addition of normal HDL, a scavenger of oxidized phospholipids, but not by HDL from patients with L-lep. The accumulation of host-derived oxidized phospholipids in L-lep lesions is strikingly similar to observations in atherosclerosis, which suggests that the link between host lipid metabolism and innate immunity contributes to the pathogenesis of both microbial infection and metabolic disease".

It may be observed that the findings in reported in references 1-11 are fully consistent with Table 1 under the heading MTL and provided important experimental evidence for the mentioned theory.

On the treatment of leprosy

Let us first discuss some details of general validity. It may be accepted that the deposition of administered antioxidants may explain the clinical improvement of patients, through their slow release from tissues, many months after the discontinuation of sulfone treatment, of administered antioxidants. Also, leprosy "chemotherapy" only consists in the stabilization of organic lipids through the administration of antioxidants and thus is understood, as bacillary resistance does not exist, that treatment acts on the auto-oxidative disease and not on the bacillus. It also explain why anti-leprosy therapeutic activity is achieved by administering the antioxidant at doses and intervals different from those used for chemotherapies that require permanent and useful plasma levels. The objective of eradicating all bacilli in leprosy patients, so sought and yearned by

leprologists, has no significance or meaning, because while auto-oxidative disease persists the patient will get sick again in case of a new contact with bacilli, which is common in an endemic environment. Only definite and permanent stabilization of organic lipids, through the mentioned mechanisms, will prevent new recurrences. The search for new anti-leprosy "chemotherapy agents" should not be done within the family of chemical compounds with antibacterial activity, but in that of compounds used as industrial antioxidants, in order to prevent auto-oxidation of natural or synthetic rubber, gasoline or fatty foods. Many sulfones, thiocarbanilides, phenothiazines, thiosemicarbazones, to which "these chemotherapics" belong, are used as industrial antioxidants.

Based on the previous facts, a proposal for the treatment of leprosy may be schematized, which consists in the cure of the auto-oxidative disease or oxidative stress by normalizing the patient auto-oxidative ground or level of the antioxidant defense. Simultaneously and in parallel, this should produce the disappearance of the bacillus and the clinical cure of the disease. Based on this, it may be stated that:

1) M. leprae should not be primarily considered in the treatment of leprosy; therefore, antibiotics and chemotherapy agents play no role in the treatment of this disease, as well as any other agent with a direct antibacterial activity.
2) The oxidative process of lipids should be normalized, blurring auto-oxidative reactions as follows: a) administration of an antioxidant with low toxicity that is deposited in fatty tissues; b) limiting the intake of polyunsaturated fatty acids; c) preventing and treating any chronic hemolytic process and d) renewal and change of fatty deposits in body tissues through proper nutrition.
3) The antioxidant, to be chronically administered, should meet the following conditions: a) having high antioxidant activity, b) having low toxicity, c) showing good absorption, transport and deposition conditions in body fatty tissues and d) remain deposited with antioxidant activity as long as possible.
4) During patient treatment, antioxidant content of subcutaneous fatty tissue should be known through appropriate means, as puncture, in order to avoid an excess of antioxidant, in which case they can act as pro-oxidants.

Conclusions

Recent experimental and clinical research confirm that human leprosy originates in a metabolic disorder in patients, leading M. leprae (if present) to develop the illness. This confirms the original hypothesis by Bergel of 1947.

Confirmation of the MTL leads to the following consequences:

a) By denying the infectious nature of leprosy, in fact relativize the value of many investigations related to the infectious nature of this illness. Among these investigations we must include the following: search of the inoculation chancre; incubation period; contagion; prevention by vaccination; treatment with chemotherapy agents or antibiotics and isolation of lepers, among others.
b) As a positive consequence, it opens a new perspective in the search of a treatment of leprosy based on metabolic processes, taking advantage of the drugs currently used for the prevention and treatment of atherosclerosis, according to the experiences of Cruz et al. (11).
c) Drugs act on auto-oxidative disease and not on the Hansen bacillus: this explains why the patient suffers from frequent disease recurrences following a variable period after treatment discontinuation. Therefore, it is recommended to treat leprosy patients throughout their lives, since the contact with the bacillus is permanent and definitely susceptible to disease development.

Finally, it can be mentioned that when socioeconomic conditions of developing countries improve, allowing a full, varied and fresh diet; when transportation of food is more efficient; when storing of food at home is improved; when the intake of saturated and unsaturated fatty acids is balanced, avoiding an overt predominance of the latter; when parasitic diseases disappear, especially malaria, and when the use of antioxidants in food conservation is widespread, or in other words when oxidative stress is decreased or avoided, the auto-oxidative disease will have been effectively fought, which will result in the disappearance of lepromatous leprosy.

References

1. Rees RJ. Experimental and clinical studies on the treatment of leprosy, Int J Lepr 1970, 38: 321-325.
2. Chatterjee, BR, Antioxidants, Meny Bergel, dapsone and downgrading of Hansen's disease. The Star 1991, 51: 2-4.
3. Vijayaraghavan, R. Antioxidative effect of vitamin E in leprosy. Indian J Lepr 2002, 74: 21-26.
4. Lima ES, Roland IA, Maroja, MF, Marcon JL. Vitamin A and lipid peroxidation in patients with different forms of leprosy. Rev Inst Med Trop Sao Paulo 2007, 49: 211-214.
5. Bhadwat VR, Borade VB. Increased lipid peroxidation in l epromatous leprosy. Indian J Dermatol Venereol Leprol 2002, 66: 121-125.
6. Vijayaraghavan, R., Suribabu, C.S., Sekar, B., Krishnamurthy, K.V. et al. Antioxidant effect of vitamin E in patients of antileprosy chemotherapy. The Star 2001. 61: 12-14.
7. Reddy YN, Murthy SV, Krishnav DR, Prabhakar MC. Oxidative stress and antioxidant status in leprosy patients. Indian J Lepr 2003, 75: 3073-16.
8. Vijayaraghavan, R, Suribabu CS, Sekar B, Oommen PK, Kavithalakshmi SN et al. Protective role of vitamin E on the oxidative stress in Hansen's disease (leprosy) patients. Eur J Clin Nutr 2005, 59: 1121-1128.
9. Prasad CVB, Kodliwadmath MV, Kodliwadmath GB. Tocopherol and ascorbic acid status in leprosy. Indian J Lepr 2007, 79: 195-201.
10. Jyothi P, Riyaz N, Nandakumar G, Binitha MP. A study of oxidative stress in paucibacillary and multibacillary leprosy. Indian J Dermatol Venereol Leprol 2008. 74: 80-86.
11. Cruz D, Watson AD, Miller CS, Montoya D, Ochoa MT et al. Host-derived oxidized phospholipids and HDL regulate innate immunity in human leprosy, J Clin Invest 2008, 118: 2917-2928.
12. Sies H. Oxidative stress: from basic research to clinical application. Am J Med 1991, 91: 31S-38S.

APPENDIX I
Basic references on the metabolic theory of leprosy (from 85 published papers)

1. Fernández JMM, Bergel M. Una doctrina terapéutica basada en los procesos de oxidorreducción: su aplicación en el tratamiento de la lepra. Rev Argent Dermatosifil –Leprol 1949, 3: 513-527.
2. Bergel M. Influence of various pro-oxidant nutritional conditions in the growth in vivo of M. leprae. Leprosy Review 1959, 30: 153-158.

3. Bergel M. Leprosy and nutrition. Leprosy Review 1966, 37: 163-167.
4. Bergel M. Actividad antioxidante biológica de las sulfonas. Acta Leprol 1968, 32: 5-9
5. Bergel M. La lepra como enfermedad metabólica. Publ Centr Estudos Leprolog 1976, 5: 8-12.
6. Bergel M. Sulfone resistance and leprosy control. Japan J Lepr 1981, 50: 51-52.
7. Bergel M. Leprosy is not an infectious disease. Japan J. Lepr 1982, 51: 113-115.
8. Bergel M. Ecological considerations on the treatment of leprosy. Japan J Lepr 983, 52: 58-59.

		INFECTIOUS THEORY	MTL
	AUTHOR	G. Armauer Hansen (1873)	Meny Bergel (1988)
I	**ETIOLOGY**	Mycobacterium leprae (Hansen bacillus).	Altered metabolic-nutritive ecosystem which increases lipid peroxidations. Oxidative stress.
II	**PATHOGENESIS**	The M. leprae reproduces itself and harms tissues (specially nerves and skin) by means of degenerative, inflammatory and trophic alterations.	The products of lipid auto-oxidation are pro-inflammatory and harm tissues. They are also essential metabolites for the opportunist germ, the M. leprae.
III	**CONTAGIOSITY**	Low but existing.	Non-existing.
IV	**INCUBATION**	Average: 2 to 5 years	Undetermined period.
V	**SYMPTOMATOLOGY**	Without symptoms of infectous-inflammatory process except when complicating with acute reactional episodes (leprosy reaction)	The leprosy reaction would be the normal status, masked by the neutralization of the inflammatory hydroperoxides through the large quantities of viable Hansen bacilli.
VI	**TREATMENT**	Chemotherapy and antibiotics: dapsone, rifampicin, thalidomide and prednisone for the leprosy reaction. No dietetic or nutritional indication.	Biological antioxidants: dapsone or others. Rifampicin and other bactericidal antibiotics are contraindicated. Nutrition with antioxidant diets.
VII	**PREMUNITION**	Vaccines: with M. leprae, BCG or other mycobacteria.	Correction of the nutritional ecosystem by antioxidant diets.
VIII	**ISOLATION**	Advisable	Inoperative.
IX	**SANITARIAN HYGIENE**	Corporeal hygiene. Avoid promiscuity, crowding.	Fresh feeding. Proper preparation and storage of food.
X	**ERRADICATION METHODS**	Immunoprophylaxis and immunotherapy through vaccination.	Correction of the nutritional ecosystem through proper feeding. Use of antioxidants added to food.
XI	**TYPE OF PATHOLOGY**	Infecto-contagious.	Nutritional-metabolic
XII	**NEIGHBOUR PATHOLOGIES**	Tuberculosis. Leishmaniasis.	Diabetes. Atherosclerosis. Colagenopathies. Autoimmune diseases.

Table 1. Comparison of the infectious cause of leprosy and the metabolic cause of leprosy (MTL).

II. THE ROLE OF ANTIOXIDANTS ON THE SETTLEMENT AND DEVELOPMENT OF TUBERCULOSIS

Introduction

Since the last quarter of XIX century, tuberculosis has been considered as a paradigm of infectious disease caused by a bacillus, namely the Koch bacillus or Micobacterium tuberculosis. The same concept applies to tuberculosis and to leprosy, as discussed in Part I of this paper. Since then the medicine books in the chapters related to these diseases, say something like: "Leprosy and tuberculosis are infectious diseases caused by Hansen and Koch bacilli, respectively". Further to these definitions, it is also asserted that these diseases also need other conditions (cofactors) in order to cause these pathologies because, in their absence, the disease does not take place. These conditions are many times unspecified, vague and previous to the settlement of these bacilli in the organism. Such cofactors are the normal nutritional state, the lack of chronic ingestion of drugs, good rest, and no smoking, among others. Generally, whenever these "ignorance labels" or "cofactors" are referred to, they are grouped together with the common name of "grounds" or "ground factors" or "base conditions" or "ecologic components" or "defenses". However, these are the essential and main factors for the settlement and evolution of these pathologies.

That leaves no room for discussion that the "ground" is a very important factor to take into account regarding tuberculosis. This "ground factor" was: a) the one which made the incidence of tuberculosis in the world decline before the advent of the modern chemotherapy; b) this prevents a person infected with Koch bacillus from developing tuberculosis disease; c) the one that does not allow the development of Koch bacillus inoculated to many animal species and, d) the one that makes that the experimental inoculation of Koch bacillus causes different degrees of tuberculosis. Perhaps, the varia-

tions of these “ground factors” have been the cause of the highest mortality rate in 1995.

Taking into account the “ground factor”, that in other words can be considered as the oxidative stress situation, as an essential element in the tuberculosis pathogenesis, there are a series of factors that define the defenses of the organisms infected by Koch bacillus. Regarding cellular immunity, these factors would be cellular mediators: cytokines; the mechanisms related to the oxygen “burst”, which imply H_2O_2 production and the myeloperoxidase system; nitric oxide production; SOD glutathione peroxidase and other antioxidant enzymes; interferons; and tumor nechrosis factor. All these elements link the cellular immunity mechanisms, in relation to the tuberculosis bacillus, with the oxidative stress. Besides, antioxidant genes of the above mentioned bacillus must be added, such as for example, the thioredoxin reductase system. The interrelations among all these elements and their effects are linked to the condition of oxidative stress, and make it difficult to determine which are causes or effects.

Based on the above considerations the rationale use of antioxidants in the prevention or in the treatment of tuberculosis arises if it is considered that at least one of the elements of the pathogenesis relates to oxidative stress. In this way this element takes an outstanding rank in the “cause factor” level, as important as the Koch bacillus, as a decisive element of the tuberculosis disease. This ground is the decisive factor for which only a very few persons infected with the tuberculosis bacillus develop the disease; as well as the decrease of the mortality caused by tuberculosis which began 100 years before the modern anti-tuberculosis chemotherapy arose.

Use of antioxidants in tuberculosis treatment

Early in 1950, Bergel established the rationale use of antioxidants in the treatment of tuberculosis. A thorough analysis of the etiology and pathogenesis of tuberculosis was presented, along with the chemotherapeutic products used for its treatment. It specially referred to the relation between the partial oxygen pressure, at both environmental and tissue level, and the development of the disease. The known influence of pro-oxidant metal catalysis in the origin of tuberculosis infection was also mentioned.

Bergel (1950) stated that the basic element of the labeled "tuberculosis ground" in an alteration in the auto-oxidative processes in the organism, with the intervention of oxygen free radicals, the formation of chain reactions and with all the pathology derived from these facts. In other words, the previous existence of the condition of oxidative stress is a requirement for the development of tuberculosis. That is to say, the old "ignorance labels", such as the above mentioned, were substituted by Bergel by: oxidative stress, auto-oxidative disease, formation of oxygen free radicals, production of chain reactions and related oxidizing species. This hypothesis, which was experimentally demonstrated, allowed to replace the "ignorance labels" for precise and specific biochemical conditions and by making a re-conceptualization of Pasteur's bacterial theory (dated 1880) in the light of the later metabolic theory (Bergel, 1988), in this case applied, *mutatis mutandis*, to tuberculosis. Further bibliography by Bergel may be found in references [3-9]. Among them, the one summarising the experimental work done at the Rockefeller Institute of New York, in 1968 is important (8). Part of the summary is quoted here: "From the above mentioned experiments it can be concluded that the prooxidant diet, high in unsaturated fatty acid and low in vitamin E, increased the susceptibility of mice to experimental infections with *Mycobacterium tuberculosis,* BCG and *Mycobacterium fortuitum.* However, animals fed with the prooxidant diets are as resistant to staphylococcal and Friedländer infections and to the LPS as animals fed with standard pellets. It should be pointed out that animals gain weight equally well with all the diets described, namely the prooxidant and the standard diets". This experimental work about tuberculosis proved, for the first time in tuberculosis history, the first pathogenic factor, the oxidative stress, achieved by experimental diets in mice.

In a recent paper, Karnodle (2010), in order to face the prevention of tuberculosis concluded that "some previously unexplained aspects of the performance of the BCG vaccine in clinical trials now make sense in the context of the new model. Finally, the model suggests that the risk of developing pulmonary tuberculosis is influenced by the balance between host-generated oxidant and microbial antioxidants that activate and suppress, respectively the antigen-presentation pathways that protect the lungs". As may be appreciated, oxidized lipid metabolites are considered to be of great value in the etiology and pathogenesis of tuberculosis and above all, in its prevention.

Conclusions

As a conclusion, we can infer the advisability of adopting metabolic paradigms, not withstanding the fact that infectious paradigms, cannot be eliminated in the study of tuberculosis. It may be noticed that the infectious paradigm has not been fully successful regarding this pathology. Everything can probably be summed up by citing Grange and Zumla (1999), who made a revision of the current state of the disease and suggested the advisability of displacing the tuberculosis bacillus as "the cause" of tuberculosis toward the social factors which generate poverty and inequalities. This unusual statement of displacing the Koch bacillus status in tuberculosis and replacing it with ecologic, nutritional and metabolic factors, that are certainly involved in the condition of oxidative stress, is by itself consistent with the views in this paper.

As a consequence of the above, it is proposed that the tuberculosis ground, namely, the auto-oxidations and the antioxidants in the origin of tuberculosis, must be the subject of future research.

References

1. Bergel M. Fundamentos del empleo de los antioxigenos en el tratamiento de la tuberculosis. *Rev. Med (*Rosario) 1950, 40: 208.
2. Bergel M. Leprosy as a metabolic disease. Instituto de Investigaciones Leprológicas, Buenos Aires. 1988. (Book published by the author), 214 pp.
3. Bergel M. La desactivación de prooxigenos metálicos como punto de partida de una nueva quimioterapia en tuberculosis. *Rev. Médica (*Rosario) 1951, 41: 9.
4. Bergel M. Antioxígenos y tuberculosis. Mecanismo de acción del PAS, TBI e HAI. *Semana Médica* 1952, 101: 130.
5. Bergel M. Autooxidación de lípidos y quimioterapia de la tuberculosis. *Rev. Médica* (Rosario) 1954, 44: 273 and 1955 46: 19.
6. Bergel M. La isoniacida como un antioxígeno biológico. *Semana Médica* 1957, 110: 192.
7. Bergel M. Exacerbación de la virulencia y producción de lesiones a distancia por el BCG en ratas alimentadas con dietas prooxidantes. *Com Círc Médico* (Rosario) 1957, 20 de agosto.
8. Bergel M. The effects of prooxidant diets on some experimental Mycobacterial infections. *Leprosy Rev 1968,* 39: 15.

9. Bergel M. Actividad antioxidante biológica de la asociación antituberculosa estreptomicina-isoniacida-ácido paraaminosalicílico. *Rev Asoc Med Argent* 1970, 84: 439.
10. Karnodle DS. Decrease in the effectiveness of bacilli Calmette-Guérin vaccine against pulmonary tuberculosis: a consequence of increased immune suppression by microbial antioxidants, not over attenuation. Clin Infect Dis 2010, 51: 177-1.
11. Grange JM and Zumla A. Paradox of the global emergency of tuberculosis. *Lancet* 1999, 353: 996.