Editorial

Participation of researchers from the Brazilian Network of Tuberculosis Research in the activities of the Brazilian Journal of Pulmonology, official publication of the Brazilian Society of Pulmonology and Phthisiology

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This issue of the *Jornal Brasileiro de Pneumonologia* (JBP, Brazilian Journal of Pulmonary Medicine) is a collection of articles regarding tuberculosis (TB). It was conceived as a companion to the publication of the proceedings and conclusions of the *I Encontro Nacional de Tuberculose* (1st National Tuberculosis Forum), to be held in Brasilia from June 30 to July 3, 2004. The forum represents a milestone in the history of Phthisiology in Brazil and is the culmination of efforts by the think tank known as the *Inteligência Nacional em TB* (National TB Knowledge Base), which is composed of representatives of various entities. The *Secretaria de Vigilância em Saúde do Ministério da Saúde* (Ministry of Health, Department of Health Oversight), the *Sociedade Brasileira de Pulmonologia e Tisiologia* (SBPT, Brazilian Society of Pulmonology and Phthisiology) and the *Rede Brasileira de Pesquisa em Tuberculose* (Rede-TB, Brazilian Tuberculosis Research Network) are all represented. The impact of their actions, agreed upon in a transparent and cordial way, can be seen as much in the content of the event as in the nature of the articles published in this issue of the journal. These articles provide unequivocal evidence of the interdisciplinary and horizontal quality of Rede-TB activities. When the position of JPB associate editor for TB was created, there were only two TB-related articles under review. On May 14, 2004, Rede-TB researchers were invited, and readily agreed, to work in collaboration with the JBP. Since then, 20 original articles, 3 review articles and 2 case reports have been submitted for publication. These 25 articles address various spheres of knowledge: epidemiology (4), diagnosis (6), clinical medicine and treatment (7), operational research (4), molecular epidemiology (1), genetics (1), immunology(1) and chemoprophylaxis(1). The reviewers should be complimented on their agility, which made it possible to have a sufficient number of TB-related articles approved for publication before the deadline for this issue. Although it was not possible, in the current issue, to publish all of the TB-related manuscripts submitted, many of these extremely relevant and high-quality articles will appear in subsequent issues of the JBP.

In response to a joint proposal put forth by the governmental projects *Pólos de Educação Permanente* (Poles of Continuing Education) and *Parque Produtivo* (Productivity Estate), a re-evaluation of the functions and interrelationships among the various entities affecting TB control is currently underway. This re-assessment involves the federal Ministries of Health, Science and Technology, and Education, as well as public and private medical schools. In addition, state and municipal administrations, health councils, medical societies such as the SBPT, professional organizations such as the *Conselho Regional de Medicina do Rio de Janeiro* (CREMERJ) and nongovernmental organizations dealing with TB or HIV, as well as research networks such as the Rede-TB, were included in this project. Conferences have been held on the subjects of scientific technology and technological innovation, the accreditation status of university hospitals has been scrutinized, and the subject of university reform has been discussed in depth. The Rede-TB researchers have been working in cooperation with the SBPT, using the JBP as a communication vehicle. Their objectives are to identify shortcomings and challenges yet to be met in the fields of science, technology and technological innovation, propose directives that encourage the

expansion of scientific knowledge in the area, orient technological development and promote innovation in the manufacture of drugs, vaccines and other basic health-care materials. In addition, the project intends to bring the guidelines of the *Plano Nacional de Ciência Tecnologia e Inovação Tecnológica* (National Plan for Scientific Technology and Technological Innovation) in line with the health-care needs of the Brazilian population. It is generally accepted that the traditional concepts regarding health research should be revised. In addition to studies conducted in the clinical, biomedical and public health fields, there is a need for additional research in the areas of human sciences, applied social sciences, mathematical sciences, earth sciences, agrarian sciences and engineering. This goal will only be achieved when representatives of these various fields work in collaboration in a transparent and inclusive way in order to identify and prioritize the gaps in treatment, teaching and dissemination of technological scientific knowledge, as well as in the incorporation of new technologies.

In analyzing the articles in this issue of the JBP, it is important to remember that, in many cases, municipal administrators, state administrators, universities, university hospitals and the Central Public Health Laboratories, as well as industry officials, all contributed to the quality of the data presented. Many studies were conducted in health centers presenting minimal organizational conditions (i.e. the existence of patient-care protocols). However, in consonance with the tools of scientific methodology provided by the parent organization, the staff members of these clinics were usually able to respond to questions of practical relevance at various levels of clinical care. What follows is a summary of the articles.

RUFFINO-NETTO A. proposes a new "formula" to highlight the fact that, despite advances in the understanding of the technical, biological, clinical and epidemiological aspects, the social dimension of TB must be considered, valued and used as a quality-of-life indicator.

BARROSO EC et al. submitted a masters thesis based on a study conducted in Ceará. This is a case-control study, in which 1309 individuals in contact with 302 multidrug-resistant TB and drug-sensitive TB patients were analyzed. The data collected suggest that there is little difference between the incidence of active TB cases resulting from contact with drug-sensitive TB patients and the incidence of those resulting from contact with multidrug-resistant TB patients. Their results demonstrate the urgent need for strategies to retard the emergence of multidrug-resistant TB. Such strategies might include implementation of the "directly observed treatment strategy" (devised by the World Health Organization and currently on the Brazilian Ministry of Health list of priorities), as well as appropriate monitoring, in reference centers, of all individuals having contact with patients suspected of having multidrug-resistant pulmonary TB.

NEVES DD et al. present a doctoral thesis based on a study carried out in the city of Rio de Janeiro. In a cross-sectional study regarding diagnosis of pleural TB in patients treated at a university hospital in Rio de Janeiro, the authors analyzed clinical, radiological and laboratory-testing variables. In those patients whose adenosine deaminase (ADA) was higher than 39 U/L, sensitivity was 95% and, even when including the prevalence of lymphocytes (> 50%) in the TB diagnosis criteria, specificity was also 95%. Since diagnostic tests may be the best source of financial savings for public health services, the authors suggest that ADA testing, using the Giusti technique, be implemented in reference health centers for pleural TB treatment.

SELIG L et al. This paper was first presented as a doctoral thesis and is the result of a collaboration of the *Secretaria Estadual de Saúde* (SES, State Department of Health), *Universidade Federal do Rio de Janeiro* (UFRJ, Rio de Janeiro Federal University), *Universidade Gama Filho* and the *Liga de Estudantes* (League of Students). In this study, data from the Rio de Janeiro TB *Sistema de Informação de Agravos de Notificação* (SINAN-TB-RJ, TB Case Registry Database) and *Sistema de Informação de Mortalidade* (SIM-TB-RJ, TB Mortality Database) were cross-referenced and the medical records from five hospitals were carefully analyzed with the aid of medical students. Only 41.7% of the deaths reported in the SIM-TB-RJ between 1995 and 1998 appeared in the SINAN-TB-RJ. Approximately 26.6% of the cases of TB reported in the state of Rio de Janeiro were nosocomial (acquired in a hospital). Analysis of the medical records of in-patients showed a re-

treatment rate of 51.2% and a post-abandonment rate of 79%. Sputum smear microscopy was carried out in 67.3% of the cases and was positive in 84%. Culture for *Mycobacterium tuberculosis* (Mtb) was performed in only 8.3% of cases. The rifampin-isoniazid-pyrazinamide-ethambutol combination, which is recommended for re-treatment, was used in only 34.4% of the cases. The study demonstrates that TB is underreported, late diagnosis is common, recommended laboratory exams are underused and the guidelines of the Ministry of Health are not followed. Therefore, since these data result from a lack of TB-control strategies in practice in hospitals, there is an urgent need for change in the current public health policies, which only prioritize the treatment of primary TB. In addition, the participation of medical students made it possible to create the League of Students, which, in cooperation with the SES and with the medical schools, has been active in TB-related academic activities in the state of Rio de Janeiro.

BRITO RC et al. submitted a masters thesis based on a joint effort by the SES of Rio de Janeiro, the UFRJ and the *Universidade Estadual do Rio de Janeiro* (Rio de Janeiro State University). In a retrospective study conducted from 1996 to 1998 at a university reference hospital for the treatment of TB and AIDS, the authors observed a high (3.6%) rate of primary resistance to the rifampicin-isoniazid combination. This rate was higher than that reported in health clinics. In the multivariate analysis, primary resistance was correlated with being a health professional. These findings underscore the need to implement effective biosafety measures in hospital environments, as well as the need for the bacteriology laboratories of such reference hospitals to routinely perform culture exams and anti-TB drug sensitivity tests.

OGUSKU MM and SALEM JI present a doctoral thesis based on research conducted at the *Instituto Nacional de Pesquisas Aeroespaciais* (National Institute of Aerospace Research) in the state of Amazonas. Strains of Mtb isolated from patients were analyzed. The objective was to determine the relevance of various polymerase chain reaction (PCR) tests to diagnose TB through identification of the target DNA sequences most often reported in medical literature (IS*6110*, 38 kDa, MPB64 and 65 kDa). The protocol used in processing the clinical samples, together with the specific primers used to amplify the 123-bp fragment of the IS*6110* sequence, demonstrated greater efficacy in the diagnosis of pulmonary (paucibacillary) TB than that reported in the literature. The authors found a positivity of 92.1%, diagnostic concordance of 0.9143, co-positivity of 94.7% and co-negativity of 100%. These results demonstrate the need to consider analyzing the genetic profiles of Mtb strains from various regions of the country prior to commercializing new molecular biology techniques.

SOARES LCP et al. present a study resulting from a Masters thesis combined with findings obtained from research conducted at the UFRJ and at the *Faculdade de Medicina de Campos* (FMC, Campos School of Medicine). In 2002, a two-phase cross-sectional study using a tuberculin test (TT) was carried out involving 316 students from the FMC, which is located in a rural area of the state of Rio de Janeiro. The authors observed a higher rate of positive TTs paralleling the period of contact with active-TB patients being treated at a state hospital that is a reference center for the emergency treatment of infectious and contagious diseases (including TB). Internships at the hospital help these students meet their graduation requirements. The incidence of positive PT in the first test was 1.4%, compared with 7.9% in the second test. These results draw attention to the need for a higher level of engagement of medical schools and the affiliated university hospitals. The authors suggest that, upon entry into university, health professionals (doctors, nurses) who will come into contact with active TB in hospitals be submitted to routine investigation using the two-TT process. In addition, they recommend that, in order to identify TT conversion, these professionals be continually re-evaluated over the course of medical school, and that the chemoprophylaxis recommended in the guidelines established by the Ministry of Health be made available.

BORGES N et al. analyze data from a Masters thesis with the help of the SES of Rio Grande do Sul, the *Secretaria Municipal de Saúde de Porto Alegre* (Porto Alegre Municipal Department of Health) and the *Universidade Luterana* (Lutheran University). The authors conducted a retrospective study, compiling clinical and epidemiological data and performing molecular typing of Mtb strains

isolated from patients treated at a health clinic in Porto Alegre. The proportion of cluster strains (genotypic groupings), which suggest recent infection, was 29.1%, and the epidemiological link among them was 37.5%. Molecular biology studies, combined with clinical and epidemiological analyses such as the present study, are of great relevance since they may promote better understanding of the dynamics of TB transmission and assist local administrators in revising TB control priorities.

RIBEIRO MO et al. submitted a Masters thesis developed in cooperation with the UFRJ and Lacen SES-RS. Since it takes several weeks to receive the results of sensitivity tests, the authors carried out a study assessing the accuracy of rapid phenotyping techniques for determining resistance to rifampicin and isoniazid in Mtb strains, using redox indicators (MTT, Alamar blue) in a liquid medium. Comparing the results to the gold standard, the concordance rate was 95% and the results were obtained in 7 days, compared to 28 days using the traditional method. In light of these results, it is necessary to validate these new tests in other reference laboratories and carry out subsequent cost-effectiveness studies in order to analyze the relationship between the clinical/epidemiological data and the laboratory data. For these new tests to be utilized and commercialized in the future, it is necessary that such studies be carried out in centers accredited by the *Agência Nacional de Vigilância Sanitária* (National Agency of Sanitary Monitoring) and in compliance with the recognized standards of Good Clinical Practice and Good Laboratory Practice.

OLIVEIRA MM et al. This article is the product of a doctoral thesis, expanded upon through a joint effort by the UFRJ, the *Fundação Oswaldo Cruz* (FIOCRUZ, Oswaldo Cruz Foundation) and the health departments of the states of Rio de Janeiro and Goiás. In this original study, in our milieu, the authors analyzed the potential role of single nucleotide polymorphisms in the promoter region of the gene codifying TNF-± at the -238 and -308 positions in TB susceptibility. The -238A allele correlated significantly with TB susceptibility and severity of clinical forms (p = 0.00002). On the other hand, the -308A allele correlated significantly with protection against other pulmonary forms of the disease (p = 0.02). Further research into such correlations and Mtb virulence might confirm their value as indicators of clinical severity, especially in groups of individuals who have been recently infected and are at risk for developing the forms of TB that present high rates of morbidity and mortality.

RODRIGUES JUNIOR JM et al. The authors of this study state that DNA vaccines may become an important tool for TB control worldwide. The two antigens studied by Brazilian researchers – antigen 85 and 65-kDa mycobacterial heat shock protein (hsp65) – and analyzed in pre-clinical trials, protect against experimental infection with virulent Mtb. Immunization with hsp65 DNA not only presents therapeutic activity (capable of curing animals infected with sensitive and resistant TB) but also induces secretion of Th1-type cytokines, thereby creating a favorable environment for the long-awaited eradication of the bacillus. In addition, the innovative approach adopted by the group of researchers is worthy of note. In cooperation with the Rede-TB, this strategy has made it possible to fulfill another dream: the implementation of a system known as the *Sistema Virtuoso de Inovação Tecnológica* (Trustworthy System of Technological Innovation) in Brazil. This system creates effective and transparent interaction between the university (for invention and new ideas) and leaders in Brazilian industry (for technological innovation), such as Nanocore Biotechnology, with the support of governmental institutions. Through this joint effort it was also possible to advance studies that demonstrate the efficacy of other formulations and means of administering the vaccine.

LAPA E SILVA and NEIO BOECHAT. In this article, the authors emphasize the need to combine clinical, immunological and genetic approaches in studying the establishment of latent TB and the development of active TB, with the aim of identifying an imbalance between activating and deactivating cytokines that could affect the microbicidal function of macrophages. In addition, the authors recommend that the role of the bacilli in this context be studied since there is evidence that mycobacteria secrete proteins capable of inducing the expression of key cytokines, such as IL-10, thereby deceiving the defense mechanisms. Understanding these mechanisms may further advances in prevention as well as in the discovery of new therapeutic targets for TB control.

CRISTINA VIANA-NIERO C and LEÃO SC. These authors comment on the utility of using molecular biology techniques to differentiate between Mtb and *Mycobacterium bovis*, which is also of interest to those working in the field of veterinary medicine. In European strains, the authors show the results from their analysis of a new marker, the mtp40 genomic fragment, that is exclusive to Mtb and absent from the *M. bovis* genome. The authors suggest that this marker be analyzed in combination with other markers in mycobacterium strains isolated in various regions of the country for the differential diagnosis between Mtb and *M. bovis*.

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