

Moving Closer to Tuberculosis Elimination through Institutional Scientific Collaboration: Opportunities for Cuba and the USA

Helena J. Chapman MD MPH PhD, Luisa A. Armas-Pérez MD MS, Michael Lauzardo MDMS, Edilberto R. González-Ochoa MD PhD

ABSTRACT

Global efforts to eliminate tuberculosis by 2050 continue to challenge health systems. In countries with low reported tuberculosis incidence, such as the USA (3.1/100,000 population) and Cuba (6.9/100,000), differences in classification by income level and health systems' overall organizational structure are evident. However, the two countries' low tuberculosis incidence, geographic proximity, robust research capacity and shared health priority for tuberculosis elimination provide fertile territory to strengthen collaboration for tuberculosis control in clinical, laboratory and community settings. Two tuberculosis symposia in Cuba—one at the

Cuba Salud Convention in 2015 and the other at the International Forum on Hygiene and Epidemiology in 2016—were instrumental in stimulating dialogue on continued efforts towards eliminating tuberculosis by 2050. In this article, we describe tuberculosis burden in the USA and Cuba, critically analyze strengths and challenges experienced in areas of low tuberculosis incidence and provide recommendations for future institutional collaboration to support tuberculosis elimination and improved population health.

KEYWORDS Tuberculosis/epidemiology, *Mycobacterium tuberculosis*, prevention, communicable disease control, disease eradication, disease elimination, international cooperation, Cuba, USA

INTRODUCTION

Globally, tuberculosis (TB) is the main infectious cause of death, with an estimated 10.4 million new cases and 1.7 million deaths in 2016.[1] An estimated one third of the world's population has asymptomatic *Mycobacterium tuberculosis* infection.[1] Over the past decade, although advances in diagnosis and treatment access, availability and effectiveness have improved TB patient outcomes, there have been no major strides towards global TB elimination. Continued emphasis on understanding the influence of political and social determinants of health on physical, psychosocial and individual health of TB patients will be crucial for TB elimination.

Three biological and social challenges in *M. tuberculosis* control persist and hinder TB elimination. First, both multidrug-resistant TB (MDR-TB), defined as *M. tuberculosis* strains that are resistant to isoniazid and rifampicin, and extensively drug-resistant TB, defined as MDR-TB resistant to any fluoroquinolone (e.g., levofloxacin, moxifloxacin) and at least one of three injectable second-line drugs (amikacin, capreomycin, kanamycin), have challenged successful treatment regimen delivery and outcomes. This human-made phenomenon is attributed to inadequate treatment by health care providers and lack of patient adherence to treatment regimens. An estimated 490,000 new MDR-TB cases were reported in 2016.[1]

Second, persons diagnosed with latent tuberculosis infection (LTBI) have an increased risk of developing active TB (TB reactivation), with a 5%–10% lifetime risk.[2] One third of the world's population is thought to harbor LTBI; it is from this pool of infected persons that active TB cases emerge. Mathematical models of TB elimination all point to the need to address LTBI in order to have any prospect of eliminating TB this century.[3]

Third, nosocomial spread of TB is also a major driver of TB transmission, especially to persons with immune deficiencies (e.g., HIV/AIDS) or living in impoverished and overcrowded

conditions (e.g., displaced populations or refugees, residents of correctional facilities or homeless shelters). Such persons frequently experience social stigma or exclusion, stress and anxiety, and demonstrate reduced health-seeking behaviors.[4] Moreover, health care workers, who have increased occupational risk of *M. tuberculosis* exposure, may be employed in health institutions with poor TB infection control practices.

Despite these general challenges, low-incidence countries, characterized by TB incidence of <100 cases per million population, have sustained TB control efforts.[5] Pragmatically speaking, obstacles to TB elimination in low-incidence countries are primarily: a) limited government support, such as inadequate health budgets; b) frequent periodic TB outbreaks in vulnerable groups (e.g., in correctional facilities, homeless shelters, health institutions); and c) need for early identification of susceptible individuals with LTBI and at risk of developing active TB.[5] Rapid responses are essential to address these challenges and act promptly to mitigate TB outbreaks and disease propagation in the community.

WHO reported 274,000 TB cases (27/100,000 population) in 2016 in the Americas Region.[1] Although the TB targets of the 2015 Millennium Development Goals were met, TB continues to be a major public health issue in Latin America and the Caribbean.[6] In 2016, two neighboring countries reported low TB incidence: USA (3.1/100,000 population) and Cuba (6.9/100,000 population).[7] Yet, although these two countries are in the TB pre-elimination stage (<10 TB cases per million population/year), further progress

IMPORTANCE The USA and Cuba—both characterized by low tuberculosis incidence, geographic proximity, robust research capacity and shared health priority for TB elimination—can strengthen institutional scientific collaboration to contribute to achieving tuberculosis control and elimination by 2050.

will be required to reach TB elimination (<1 TB case per million). [8] While the USA and Cuba differ in terms of total population and allocated budgets for their National TB Programs (NTP), their comparable levels of estimated TB incidence coupled with TB control as a shared national priority provide a framework for future scientific TB collaboration and partnerships. Table 1 presents estimated indicators of TB burden, treatment and NTP financing for both countries in 2016.[7,9] National surveillance programs have reported variation in TB incidence within each country. Table 2 displays TB incidence in 2015 and 2016 for US states and Cuban provinces reporting ≥ 3 cases per 100,000 population.[10,11]

Table 1: Reported TB cases, treatment and national budgets, USA and Cuba, 2016

Indicator	USA	Cuba
Total population, 2016 (millions)	322	11
Country income level	High	Upper middle
TB burden, 2016		
Incidence rate (per 100,000 population)	3.1	6.9
Mortality rate (per 100,000 population)	0.03	0.09
Number of reported new and relapse cases (total)	8814	689
Number of MDR-TB cases (total)	130	16
New cases (%)	1.5	2.2
Previously treated cases (%)	5.6	4.2
TB treatment coverage*, 2016 (%)	87	87
TB treatment success rate, 2015 (%)		
New and relapse cases	83	83
Previously treated cases, excluding relapse cases	77	50
TB financing, 2016		
National TB budget (US\$ million)	142	27

*new and relapse TB cases notified and treated, divided by estimated incident TB cases
MDR: multidrug-resistant TB: tuberculosis
Sources: references 7,9

Continued discussions of global TB burden prompted the World Health Assembly to adopt the WHO End TB Strategy in 2014, and shift the dialogue from “stopping TB” to “ending the TB epidemic.”[5] This strategy emphasizes a holistic approach, adopting multisectoral interventions for community health and society, with three main pillars: 1) enhanced patient-centered prevention and treatment (e.g., early diagnosis and treatment of high-risk groups); 2) national policies and supportive systems (e.g., political commitment, community engagement and appropriate health policies); and 3) targeted research and scientific advances (e.g., discoveries to identify innovative strategies and approaches).[5]

Considering this holistic approach with its pillars, collaborative scientific teams are key to advancing the technical agenda and making progress towards TB elimination. In this report, we propose that the USA and Cuba—which have low TB incidence, geographic proximity, robust research capacities, and shared health priorities aimed at TB elimination—can strengthen scientific collaboration for TB control in clinical, laboratory and community settings. Considering TB control efforts in the USA and Cuba, we aim to critically analyze the strengths and challenges experienced in these two low-incidence countries and provide recommendations for future institutional collaboration that can contribute to TB elimination and improved population health.

Table 2: Tuberculosis incidence $\geq 3/100,000$ population^a, USA and Cuba, 2015–2016

Jurisdiction	2015 n (rate)	2016 n (rate)
USA^b (state or district)		
Georgia	320 (3.2)	(<3.0)
Arkansas	90 (3.0)	91 (3.0)
Minnesota	(<3.0)	168 (3.0)
Florida	602 (3.0)	639 (3.1)
New Jersey	326 (3.6)	294 (3.3)
Washington, DC	33 (4.9)	25 (3.7)
Maryland	(<3.0)	220 (3.7)
New York	763 (3.9)	768 (3.9)
Texas	1333 (4.9)	1250 (4.5)
California	2130 (5.5)	2073 (5.3)
Alaska	68 (9.2)	57 (7.7)
Hawaii	127 (8.9)	119 (8.3)
Cuba^c (province)		
Camagüey	20 (2.6)	23 (3.0)
Matanzas	26 (3.7)	22 (3.1)
Guantánamo	24 (4.7)	16 (3.1)
Sancti Spiritus	27 (5.8)	17 (3.6)
Cienfuegos	32 (7.8)	16 (3.9)
Pinar del Río	29 (4.9)	25 (4.3)
Holguín	45 (4.3)	46 (4.4)
Artemisa	20 (4.0)	26 (5.1)
Santiago de Cuba	46 (4.4)	55 (5.2)
Villa Clara	70 (8.9)	52 (6.6)
Granma	45 (5.4)	57 (6.8)
Las Tunas	29 (5.4)	40 (7.4)
Havana	199 (9.4)	200 (9.4)
Ciego de Ávila	46 (10.7)	45 (10.4)
Mayabeque	34 (8.9)	47 (12.3)

^a $\geq 3/100,000$ population selected as baseline because 2015 national TB incidence in the USA was 3/100,000 population

^bnumber of reported cases (US National Tuberculosis Surveillance System) divided by midyear population estimates (US Census Bureau)

^cnumber of reported cases (Cuban Ministry of Public Health National Medical Records and Health Statistics Division) divided by population estimates (Cuban Ministry of Public Health statistical yearbooks)

incidence: new and relapse cases in past year
TB: tuberculosis

Sources: references 1,10,11

PROPOSED COLLABORATION

Background This proposed bilateral collaboration in TB control originated from four scientific exchanges since 2014, all with Cuban government approval. In March 2014, participation in the American Public Health Association–Medical Education Cooperation with Cuba (APHA–MEDICC) delegation provided an immersion experience to gain insight into Cuba’s universal health coverage as it functions at the primary care level. Following this exchange, the Cuban Hygiene and Epidemiology Society’s Pulmonary Health Executive Board and the Pedro Kouri Tropical Medicine Institute (IPK), a PAHO/WHO collaborating center, successfully conducted two TB symposia at international conferences in Havana in 2015 and 2016: the International TB Symposium 2015 (Towards TB Elimination 2016–2050),[12] at Cuba Salud 2015 in April 2015, and the International Symposium on Pulmonary Health and TB Elimination (TB Elimination: Accelerating the Pace), held in conjunction with the International

Forum on Hygiene and Epidemiology, in November 2016. Both symposia were instrumental in stimulating dialogue on continued efforts towards TB elimination by 2050.[12] Finally, in April 2017, Cuban health leaders and invited international researchers participated in the workshop, Epidemiologic and Operational Research on TB, at IPK.

These events provided opportunities for fruitful scientific and technical exchange among clinicians and health researchers at IPK and the University of Florida (UF), with two notable results: First, Helena Chapman, then a UF doctoral student, received a three-week cross-cultural training in clinical and epidemiologic aspects of TB, mentored by respected clinicians and researchers at IPK and other Cuban Ministry of Public Health (MINSAP) institutions. Second, a collaborative manuscript was published that described the outcomes of the International TB Symposium 2015.[12] Such academic exchanges are evidence of strong commitment to scientific discovery, research and practice en route to TB control and elimination.

The proposed collaboration can strengthen future scientific advances in TB prevention and control efforts, which would be beneficial locally, nationally and internationally, and serve as a model for other countries that aim to build scientific capacity, better understand the epidemiology of TB transmission and reach optimal indicators for population health related to TB control.

Participating Institutions UF, located in Gainesville, Florida, was founded in 1853 and has recently been ranked as one of the USA's top ten public universities. The Division of Infectious Diseases and Global Medicine forms part of the UF Health Science Center, the largest health education center in the southeastern USA. [13] In addition to academic training and clinical responsibilities in medicine and patient care, scientific research collaborations among various disciplines are fundamental at the UF Health Science Center, UF Emerging Pathogens Institute, Southeastern National TB Center (SNTC), and UF One Health Center of Excellence. SNTC itself provides services to the southeastern USA, including Puerto Rico and the US Virgin Islands. Together, these academic centers provide broad research expertise and potential for collaboration in basic, clinical and social sciences related to spread of emerging infectious diseases that influence human, animal and environmental health in Florida communities.

Located in Havana, IPK was founded in 1937 and has become an internationally renowned scientific institution for undergraduate and graduate academic training, medical care, laboratory diagnostics and research.[14] As part of MINSAP, IPK's main objectives are to provide optimal medical services to patients, conduct laboratory diagnostics of infectious pathogens, educate Cuban and international students in multiple scientific disciplines, and develop research initiatives on prevention and control of tropical and other infectious diseases. Collaborating departments include the National Tuberculosis, Leprosy and Mycobacteria Reference and Research Laboratory, IPK Hospital, Department of Epidemiology and the National Clinical Reference Center for AIDS Treatment.

Proposed activities Through this proposed collaboration, binational activities between UF and IPK clinicians and researchers in basic, clinical and social sciences related to TB control efforts can identify research gaps and develop innovative projects to

strengthen the scientific knowledge base about *M. tuberculosis*. Notably, these internationally recognized institutions, with robust clinical and research capacities in infectious diseases, have geographic proximity that would facilitate such joint work over the long term. In order to maximize scientific rigor and communication throughout an established research timeline, several activities can facilitate open dialogue, rapport among researchers, task efficiency, adherence to deadlines and overall transparency.

We propose a US-Cuban collaboration to develop a long-range strategy for research into TB epidemiology as it relates to the geographic catchment area of each institution, an accounting of best practices that have emerged in each area, analyses of persistent problems and innovative proposals to address these challenges, and a publication agenda to share findings with the scientific and public health communities. Working methods would include conference calls, web-based seminars, academic exchanges, research collaborations and joint publications.

ANALYSIS

Strengths Since NTPs were founded in the USA and Cuba, efforts towards TB elimination have integrated essential components of TB control. Political commitment can be described in the context of government responsibility, accountability and rapid responses to TB epidemics.[15,16] The US Public Health Service's NTP was established in 1944, eventually transitioning financial support from local and state governments to the federal level.[15] In Cuba, the national TB surveillance system was initiated in 1953. [16] Cuba's NTP was established in 1959, and national policies and guidelines were implemented in 1963 and 1964, focusing on population-based health promotion and disease prevention for TB control.[16] Notably, neonatal BCG vaccination has been a routine preventive measure in Cuba,[17] but not in the USA.

All countries have encountered challenges in managing MDR-TB, diagnosing and treating LTBI, and identifying and preventing TB transmission in high-risk population groups. However, rapid and effective responses to these challenges by NTPs in the USA and Cuba have demonstrated successful identification of TB cases, reduction of TB incidence and mortality, and increased treatment success rates.[18,19] Over time, robust *M. tuberculosis* monitoring and surveillance systems; universal access to directly observed treatment, short-course; and contact followup have proven to be strengths for rapid outbreak control. Strict *M. tuberculosis* infection control practices and continued research and international collaboration to understand TB dynamics complement the structure and function of these two systems. Also, promotion of human rights and ethical treatment of TB patients has aimed to reduce social stigma and discrimination that may hinder access to TB service delivery or negatively influence health-seeking behaviors.

Challenges In addition to the global challenges, TB control in low-incidence countries such as the USA and Cuba presents unique hurdles to continuing to improve TB indicators. Sustained innovative programs and collaborations that target these challenges will facilitate TB elimination.

LTBI and risk of TB reactivation Prompt identification of population groups at high risk for TB infection or disease is essential for TB control. Certain groups have risk factors for *M.*

tuberculosis exposure, such as those with occupational risks (e.g., health care workers), compromised immune systems (e.g., HIV/AIDS), comorbidities (e.g., diabetes) or toxic behaviors (e.g. tobacco use) that also lead to higher risk for TB infection or reactivation.[8]

Migration from high-burden to low-burden countries Low-incidence countries, which have less active TB transmission than high-incidence countries, have documented TB transmission based on immigration.[8] Migrants may have previous *M. tuberculosis* exposure from their country of origin; their latent infections can progress to active TB disease following a stressful relocation and settlement process, and further increase population risk of exposure.

Delayed identification and treatment of TB cases Delays in health care service delivery to diagnose TB can be attributed to health providers (e.g., medical error) or patients (e.g., reduced health care-seeking behavior due to stigma, mistrust of authorities or lack of service availability or access to health institutions).[18] It is thus essential to avoid missed opportunities to identify TB infection or disease in the general population.

Expertise in TB control Low TB incidence may result in fewer professionals having direct experience with TB, which may lead to gaps in health professions education and training, contributing to medical errors, lapses in infection control practices, or inadequate outbreak control and contact followup.[18] Existence of and adherence to administrative, environmental and respiratory protection controls in *M. tuberculosis* are crucial to reduce nosocomial TB transmission in health institutions.

Type of institution Although UF and IPK are both institutions that focus on scientific advances in clinical and research capacities, they have differing characteristics. UF is a public (state) academic institution of higher learning, forming part of Florida's state university system, and includes SNTC's state and regional scope. IPK is a public (national government) institution, under MINSAP, with academic functions as well as clinical responsibilities at municipal, provincial and national levels.

US embargo against Cuba In 1961, the US Congress passed legislation forbidding assistance to communist countries, including Cuba, and authorized the President to embargo all trade with Cuba. The embargo was formally declared on February 3, 1962 and has since limited direct interactions between the two countries, impeding trade and commerce, economic relations, and aid and development, and making scientific collaboration challenging.[20] Despite such restrictions, academic exchanges in clinical practice and research activities over the past decade have fostered an open scientific dialogue between US and Cuban scientists.

Next steps and recommendations Challenges in TB control encountered in low-incidence countries will continue, so collaborative efforts between the USA and Cuba need to take a holistic approach towards reducing TB burden, emphasizing the importance of understanding all determinants that influence physical and psychosocial health outcomes related to TB, is imperative for clinicians and researchers leading efforts towards TB elimination. Hence, targeted efforts to reduce risk of *M. tuberculosis* transmission can be multidisciplinary in nature in

clinical and community settings. Passive and active surveillance of active TB cases can rapidly identify persons with TB infection or disease, reducing diagnostic delay, enabling timely preventive or curative therapy as needed, and increasing the proportion of cases successfully treated. Likewise, rapid identification of social or structural barriers in health care service delivery can improve understanding of TB dynamics and serve to strengthen established TB control policies. Next steps in TB control, incorporating scientific evidence to inform policy, include:

Renewal of political commitment to TB elimination It is essential to understand the structural determinants of TB control based on federal or national policies and directives that drive legal regulations and budget allocation. NTPs require administrative leadership and financial resources to maintain universal access to and availability of TB service delivery in all institutions and communities.

Implementation of new technologies to facilitate TB diagnostics and treatment Development of new technologies, whether in laboratory diagnostics or more effective treatment regimens, is key to prompt diagnosis and treatment of TB infection and disease.

Promotion of sustainable training and evaluation Continued training in basic, clinical and social sciences can advance scientific and social understanding of *M. tuberculosis* and transmission dynamics, yet can be difficult in the face of an epidemic with decreasing incidence rates. Highlighting barriers among health care workers or community members that may hinder components of TB service delivery can support formulation of more efficient designs or alternative approaches for holistic care.

Quality assurance of monitoring and evaluation in TB control Close examination of TB control through monitoring and evaluation procedures can identify poor quality or gaps in practice so that they can be modified. By identifying discrepancies in TB burden among states or provinces, preventive actions and prioritized medical attention can be concentrated on the geographic sites most in need.

Focus on LTBI Current TB control efforts and economic development have helped reduce active TB incidence, but to ultimately eliminate TB, a much greater focus on testing and effective treatment of LTBI is critical. Scaling up LTBI services will require operational and clinical research to inform new policies.

CONCLUSIONS

Countries with low TB incidence, such as the USA and Cuba, have made successful strides in the move to eliminate TB by 2050. Their collaboration can serve as a model for other countries that intend to reach population health targets for TB, improve understanding of TB epidemiology, and strengthen academic capacity-building and training of basic, clinical and social scientists. With close geographic proximity, research capacity and shared health priority for TB elimination, the two nations can collaborate and share clinical, laboratory and community health experiences to accelerate TB elimination throughout the Americas Region. 

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2017. WHO/HTM/TB/2017.23. Geneva: World Health Organization; 2017. 147 p.
2. Chapman HJ, Lauzardo M. Advances in diagnosis and treatment of latent tuberculosis infection. *J Am Board Fam Med.* 2014 Sep–Oct;27(5):704–12.
3. Hill AN, Becerra J, Castro KG. Modelling tuberculosis trends in the USA. *Epidemiol Infect.* 2012 Oct;140(10):1862–72.
4. Figueroa-Muñoz JI, Ramon-Pardo P. Tuberculosis control in vulnerable groups. *Bull World Health Organ.* 2008 Sep;86(9):733–5.
5. World Health Organization. Implementing the End TB Strategy: The essentials. WHO/HTM/TN/2015.31. Geneva: World Health Organization; 2015. 130 p.
6. Rendon A, Fuentes Z, Torres-Duque CA, Granado MD, Victoria J, Duarte R, et al. Roadmap for tuberculosis elimination in Latin American and Caribbean countries: a strategic alliance. *Eur Respir J.* 2016 Nov;48(5):1282–7.
7. World Health Organization. Tuberculosis country profiles, 2016 [Internet]. Geneva: World Health Organization; 2017 [cited 2018 Jan 26]. Available from: <http://www.who.int/tb/country/data/profiles/en/>
8. World Health Organization. Towards tuberculosis elimination: An action framework for low-incidence countries. WHO/HTM/TB 2014.13. Geneva: World Health Organization; 2014. 67 p.
9. The World Bank. World Bank Open Data [Internet]. Washington, D.C.: The World Bank; c2017 [cited 2018 Jan 26]. Available from: <http://data.worldbank.org/>
10. Schmit KM, Wansaula Z, Pratt R, Price SF, Langer AJ. Tuberculosis - United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2017 Mar;66(11):289–94.
11. National Health Statistics and Medical Records Division (CU). Anuario Estadístico de Salud, 2016 [Internet]. Havana: Ministry of Public Health (CU); 2017. 206 p. Available from: http://files.sld.cu/dne/files/2017/05/Anuario_Estad%C3%ADstico_de_Salud_e_2016_edici%C3%B3n_2017.pdf. Spanish.
12. Chapman HJ, Armas Pérez L. Innovative Tuberculosis Symposium held during Cuba Salud 2015. *Tuberculosis (Edinb).* 2016 Dec;101:41–3.
13. University of Florida. Division of Infectious Diseases and Global Medicine [Internet]. 2017 [cited 2017 Nov 20]. Gainesville (US): University of Florida; c2018 [cited 2017 Nov 20; updated 2018 Mar 1]. Available from: <http://id.medicine.ufl.edu/>
14. Pedro Kourí Tropical Medicine Institute [Internet]. Havana: Pedro Kourí Tropical Medicine Institute; c1999-2018 [cited 2017 Nov 20]. Available from: <http://instituciones.sld.cu/ipk/informacion-del-ipk/>. Spanish.
15. Binkin NJ, Vernon AA, Simone PM, McCray E, Miller BI, Schieffelbein CW, et al. Tuberculosis prevention and control activities in the United States: an overview of the organization of tuberculosis services. *Int J Tuberc Lung Dis.* 1999 Aug;3(8):663–74.
16. Beldarrain E. Impact of the 1970 reforms to Cuba's national tuberculosis control program. *MEDICC Rev.* 2015 Jul;17(3):33–8.
17. Galindo BM, Concepción D, Galindo MA, Pérez A, Saiz J. Vaccine-related adverse events in Cuban children, 1999–2008. *MEDICC Rev.* 2012 Jan;14(1):38–43.
18. Taylor Z, Nolan CM, Blumberg HM; American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2005 Nov;54(RR-12):1–81.
19. González E, Armas L, Llanes MJ. Progress towards tuberculosis elimination in Cuba. *Int J Tuberc Lung Dis.* 2007 Apr;11(4):405–11.
20. Drain PK, Barry M. Fifty years of U.S. embargo: Cuba's health outcomes and lessons. *Science.* 2010 Apr 30;328(5978):572–3.

THE AUTHORS

Helena J. Chapman (Corresponding author: Helena.Chapman@medicine.ufl.edu), physician specializing in public health, with a master's degree in public health (epidemiology) and doctorate in public health (One Health). Division of Infectious Diseases and Global Medicine (DIDGM), College of Medicine, University of Florida (UF), Gainesville, Florida, USA.

Luisa A. Armas-Pérez, pulmonologist with a master's degree in epidemiology. Associate researcher and associate professor, Department of Epidemiology, Pedro Kourí Tropical Medicine Institute (IPK), Havana, Cuba.

Michael Lauzardo, internist and pulmonologist with a master's degree in epidemiology. Associate professor, DIDGM, UF College of Medicine, Gainesville, Florida, USA.

Edilberto R. González-Ochoa, physician epidemiologist with a doctorate in health sciences. Full professor and senior researcher, Department of Epidemiology, IPK, Havana, Cuba.

Submitted: October 27, 2017
Approved for publication: March 7, 2018
Disclosures: None

Cuban Epidemic Neuropathy: Insights into the Toxic–Nutritional Hypothesis through International Collaboration

Alina González-Quevedo MD PhD, Rosaralis Santiesteban-Freixas MD PhD, Janis T. Eells PhD, Lucimey Lima MD PhD, Alfredo A. Sadun MD PhD

ABSTRACT

From 1991 to 1993, an epidemic of optic and peripheral neuropathy—the largest of the century—broke out in Cuba, affecting more than 50,000 people. Initially the main clinical features were decreased visual acuity, central and cecocentral scotomas, impaired color vision and absence of the papillomacular bundle. Later, peripheral and mixed optic–peripheral forms began to appear. Due to the magnitude of the epidemic, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. PAHO and WHO immediately responded by sending a mission of international experts. Several hypotheses regarding the pathogenesis of Cuban epidemic neuropathy were put forward including: toxic, nutritional, genetic and infectious. The authors refer to extensive studies by researchers sponsored by the Cuban government and PAHO/WHO, joined by scientists from several other countries, including the USA. This paper describes their multidisciplinary work, particularly devoted

to investigating the hypothesis of a primary toxic–nutritional cause of the epidemic. Clinical aspects, such as case definition and clinical description, were vital issues from the start. Cuban physicians who first examined patients received a clear impression of its toxic–nutritional origin, later confirmed by international experts. Research then focused on the mechanisms contributing to damage under the toxic–nutritional hypothesis. These included injuries to the mitochondrial oxidative phosphorylation pathway, nutritional deficiencies, excitotoxicity, formate toxicity and dysfunction of the blood–brain barrier. It was expected that the results of such international collaboration into this major health problem would also shed more light on mechanisms underlying other nutritional or tropical myeloneuropathies.

KEYWORDS Optic neuritis, optic neuropathy, peripheral neuropathy, neurotoxicity syndromes, disease outbreaks, international cooperation, Cuba

INTRODUCTION

The outbreak of optic and peripheral neuropathy in Cuba at the beginning of the 1990s affected more than 50,000 persons throughout the country.[1] The epidemic followed an abrupt economic crisis due to the collapse of the socialist bloc (1989–1991) and the tightening of the US embargo, which led to severe food shortages and greater physical demands on the population (motor-driven transportation was at a near standstill). These deprivations were the underlying factors in what became the largest epidemic of neurological disease in the 20th century.[2]

The first cases were reported in Cuba's westernmost province, Pinar del Río, towards the end of 1991: patients presented bilateral vision loss, suggesting a diagnosis of retrobulbar neuritis. As case numbers continued to climb, in April–June 1992, Cuba's Ministry of Public Health (MINSAP) sent a multidisciplinary commission to examine the patients in the field. Visual deficits described included decreased visual acuity and color perception, and/or central or cecocentral scotomas, with a normal fundus or slight temporal pallor of the optic nerve. In some cases, neurological impairments such as a predominantly sensory peripheral neuropathy and hearing loss were observed. Cuban scientists began investigating the possible etiology and hypothesized that the cause was probably multifactorial, with emphasis on nutritional and toxic factors,[3] without ruling out

a possible viral contribution, based on virologists' findings from cerebrospinal fluid (CSF) studies.[4]

After months of research, two types of neuropathy were defined: an optic form (characterized by subacute onset of the symptoms and signs previously described) and a peripheral form, a predominantly sensory neuropathy, with posterior spinal cord involvement in some cases, with or without concurrent optic neuropathy. The optic form was more prevalent in men, the peripheral form in women. Both forms were often accompanied by weight loss and fatigability. Incidence rates were 926.7 per 100,000 population for persons aged 45–65 years and 290.9 per 100,000 for persons aged >65 years, lowest in children aged <15 years, 4.2/100,000.[3] The epidemic spread from west to east with the highest incidence rates in Pinar del Río Province (1332.8/100,000) and lowest in Guantánamo, Cuba's easternmost province (65/100,000). Risk was associated with smoking; lower body mass index; and lower intake of animal protein, fat, and foods containing B vitamins. Beginning 1993, Dr Hector Terry Molinert (then MINSAP's Vice Minister for Epidemiology) and his team proposed distribution of vitamin supplements (including B vitamins) to the entire population. After this was implemented, the epidemic began to decline as of May 1993.[3] At first, the disease was named Cuban epidemic optic neuropathy, but as peripheral nervous system involvement became apparent, a more general term was applied: Cuban epidemic neuropathy (CEN).[5]

IMPORTANCE Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can help solve important health problems, in this case, shedding light on other metabolic or mitochondrial optic neuropathies.

Due to CEN's scale as a public health problem, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. Among the first to arrive in Cuba to investigate the outbreak through the US-based International Peace for Cuba Appeal were Norah Lincoff and Michio Hirano, who examined patients between May 4 and 11,

Lessons in International Cooperation

1993, and soon published their impressions of the epidemic.[6] Almost simultaneously, PAHO and WHO responded by sending missions May 16–26 and June 16–24, 1993, briefed on arrival by Cuban experts in nutrition, toxicology, ophthalmology, neurology and epidemiology. The missions' objectives were mainly to review and analyze available information regarding CEN's clinical and epidemiological features and possible causes, and to recommend and collaborate in research areas that could be useful to determine etiology and eventual control. US scientists from various clinical and scientific backgrounds who participated in the PAHO/WHO missions published a detailed account in 1997.[7]

The information gathered by Cuban and international experts who visited the country from May 1993, was presented at the International Workshop on Cuban Epidemic Neuropathy, held in Havana in July 1994. At that time, the main conclusion was that inflammatory or infectious origins were unlikely. Morphologic changes were consistent with an axonal neuropathy, similar to that observed in toxic–metabolic, or nutrition deficiency conditions. The Workshop emphasized the need to continue investigating and to design further studies with a multidisciplinary and multicenter approach.[8]

The Role of International Collaboration A vast program was established between MINSAP, PAHO/WHO, Orbis International, CDC, US NIH and other international organizations to investigate CEN's causes. Experts from Cuba, the USA and Venezuela collaborated in studying CEN's clinical, toxicologic and neurochemical characteristics in order to understand its underlying mechanisms. The authors' experience reported in this paper are related to joint work carried out in patients in Pinar del Río during the epidemic period and later in development of models of low-dose chronic methanol administration in experimental animals.

OBJECTIVES

1. Describe the clinical ophthalmological and neurological characteristics of the CEN epidemic in patients residing in Pinar del Río Province.
2. Propose a pathophysiological hypothesis for CEN etiology.

Justification The CEN investigation was started early in 1992 by Cuban scientists and continued from May 1993 in collaboration with scientists mainly from the USA, but also from the United Kingdom, Venezuela, Russia and elsewhere. The need to identify the possible causes or contributing factors generating this unique disease outbreak led to an extensive research network that would eventually investigate various hypotheses about the epidemic's origins.

Participating institutions Researchers from Cuba's Neurology and Neurosurgery Institute (INN) studied CEN in Pinar del Río Province during the first quarter of 1992. Rosaralis Santiesteban Freixas (RSF), head of the Neuro-Ophthalmology Department, and Santiago Luis (SL), neurologist and Director of the Institute, carried out extensive clinical examinations of CEN patients, while Alina González-Quevedo (AGQ) and Ileana Alfaro, of the Neurochemistry and Neuroimmunology Laboratory, conducted serum and CSF studies.

Alfredo Sadun (AS) was a member of the PAHO/WHO delegation (at the time, professor of ophthalmology and neurosurgery at the Doheny Eye Institute, University of Southern California, Los Angeles, USA). He travelled to Cuba in May and September 1993 to perform clinical assessments on a small number of CEN patients. In 1994, he visited Cuba twice again, the second time accompanied by Janis Eells (JE), professor of pharmacology and an international expert in methanol toxicity at the Department of Pharmacology and Toxicology, University of Wisconsin–Milwaukee, USA.

Two years later, after the epidemic had subsided, Dr Lucimey Lima (LL), an expert in basic retinal and optic nerve neurochemistry, participated in a scientific meeting in Cuba and subsequently joined the research group.

Mechanisms Collaboration with US colleagues began in 1993–1994 under the aegis of a larger cooperation effort between MINSAP and PAHO/WHO. Financial support came from PAHO, Orbis International, and US NIH. Collaboration with Venezuelan colleagues in 1997–2002 was supported by grants and fellowships from Venezuela's National Foundation for Science, Technology and Innovation (Grant S1-2001-903) and the Scientific and Technological Research Council (Grant S1-723, fellowship from Project PI-3277, scholarship PI-98-3277).

Activities

- **April–June 1992:** clinical and physical ophthalmological examinations in Pinar del Río Province, neurological examinations of patients, serum and CSF sample collection
- **May and September 1993:** clinical and physical ophthalmological examination of 20 patients in Pinar del Río, reassessment of patients in September, analysis of methanol content in sample of home-brewed rum from Pinar del Río
- **1994:** formate and folate analysis of serum and CSF samples stored at INN, histological analysis of four sural nerve and one optic nerve biopsy from CEN patient
- **1995:** development of a rat model of chronic methanol intoxication by AS (in USA) and rat/human comparative histological studies
- **1998–2000:** development of a rat model of chronic methanol intoxication by AGQ (in Venezuela) and neurochemical studies

Ethics Studies conducted in human subjects and animal experimentation were approved by the ethics committees of Cuba's INN and the Venezuelan Institute of Scientific Research and were conducted according to the Declaration of Helsinki for experimentation in human subjects and animals. [9] Participants gave written informed consent.

ANALYSIS

In response to Cuba's request and PAHO/WHO's call, several cooperative initiatives were planned and carried out jointly by US, Latin American and Cuban researchers.

Clinical findings Researchers from Cuban institutions started investigating the neuropathy outbreak from its onset in Pinar del Río Province. RSF carried out ophthalmological examinations, for which a protocol was established in April–May 1992. As a result, visual impairment was described as follows:[10,11]

- Bilateral decreased near and far visual acuity, not corrected with lenses
- Impaired red–green color vision on the Ishihara test[12]
- Bilateral and symmetrical central and cecocentral scotomas, especially for red and green, in tangent field testing
- Normal fundus examination or slight temporal optic disc pallor

The first cases were mainly men aged 25–64 years, heavy smokers and/or alcohol consumers, who complained of blurred vision, light sensitivity and weight loss. This, together with the ophthalmological findings, pointed to an initial diagnosis of tobacco–alcohol amblyopia.[13]

In May–June 1992, more Cuban experts visited Pinar del Río (biostatisticians, epidemiologists, neurologists and nutritionists, among others). By then, the morphology of visual evoked potentials was also found to be altered, displaying a bifid p100 wave. Neurological signs and symptoms were also detected in some patients with optic neuropathy, consistent with a predominantly sensory peripheral neuropathy: hearing loss, deep tendon hyperreflexia indicating corticospinal tract involvement, and increased urinary frequency, urgency in urinating and in some cases urinary incontinence.

Three forms of neuropathy were identified: optic, peripheral and optic–peripheral. Later, cases were also reported in other provinces with an apparent pattern spreading from west to east. House-to-house surveys and case–control studies in Pinar del Río reported vision improvement in most cases when patients were treated with B-complex vitamins. The multidisciplinary commission's hypothesis was that the epidemic stemmed from toxic–nutritional causes. Although a viral contribution was not ruled out at the time, the epidemiological pattern was inconsistent with that of a communicable disease.[13]

Venezuelan neuro-ophthalmologist, Rafael Muci, a PAHO/WHO expert who participated in the mission to Cuba in May 1993, had shown Cuban researchers the use of red-free light for fundus examination, permitting visualization of loss of nerve fiber layers in the retina. In December 1992, his expertise had been requested by Cuban neuro-ophthalmologists cognizant of the need to demonstrate anatomical correlates of functional damage to the papillomacular bundle observed in visual field studies.

Alfredo Sadun and his colleagues conducted extensive neuro-ophthalmological and psychophysical examinations and interviews on 20 patients upon his arrival to Cuba with the PAHO/WHO delegation in May 1993. Several common features and patterns were subsequently determined, recommended and accepted by the Cuban epidemic task force for a new case definition.

Diagnosis required evidence of nerve fiber layer loss in the papillomacular bundle and any three of the following five symptoms and signs: subacute bilateral vision loss, dyschromatopsia, saccadic smooth pursuit, central or cecocentral visual field defect and impaired contrast sensitivity. Cuban ophthalmologists were trained by Muci in the new recommended case definition and in use of neuro-ophthalmological (red-free funduscopy) and psychophysical tests (threshold Amsler grid testing)[14] required to diagnose epidemic optic neuropathy. This considerably reduced the number of false positives.[5]

Neurochemical studies and experimental models Among the first laboratory studies conducted early in the outbreak were serum and CSF analyses to assess the possibility of immune-mediated inflammatory optic neuropathy. The results did not support this hypothesis, since only a minority of patients exhibited intrathecal IgG synthesis. These findings and CEN's epidemiological and clinical features made an infectious process unlikely.[15] Increased blood–CSF barrier permeability was observed in approximately 30% of cases, blood–CSF damage being more frequent within 16 to 60 days of disease onset and disappearing after 120 days. Blood–CSF barrier dysfunction was more prevalent in patients with severe neurological impairment but was not found to be related to severity of ophthalmological damage. These results were later confirmed in a larger sample of patients. Considering that the most favored hypothesis for CEN origin was toxic–nutritional, it was suggested that blood–brain barrier dysfunction could be associated with metabolic derangements and/or neurotoxicity.[16]

Although previous epidemiological studies indicated that intake of essential amino acids in CEN patients was below 70% of recommended values,[17] we found levels of essential amino acids were generally preserved, except for a selective reduction of taurine and threonine.[18] Serum albumin levels were also preserved.[15] Taurine, a sulfur containing neutral β amino acid, was of particular interest because of its important CNS trophic function, especially in the retina and optic nerve, as well as its antioxidant properties.[19] Taurine was lower in patients with more severe ophthalmological impairment, but was not associated with severity of polyneuropathic manifestations, indicating that taurine deficiency could play a role in the optic form's pathophysiologic mechanisms.[18] Although endogenous taurine synthesis occurs in the liver and brain (pyridoxine required as a cofactor), the human body has limited capacity to synthesize it. Thus, vitamin B6 would be considered an essential amino acid in situations of widespread vitamin deficiency. Furthermore, animal products are the main sources of taurine in humans, and these were very scarce in the Cuban diet in the early 1990s.

CEN patients' CSF displayed accumulation of glutamate and aspartate (excitatory amino acids), suggesting that excitotoxicity could also be involved in the disease's pathophysiology.[18]

In the search for toxins that may have triggered CEN, noncommercial (home-brewed) rum samples acquired in Cuba by AS were tested in the USA, revealing methanol levels from 0.87% to 1%.[5] Although this amount would not lead to acute methanol intoxication, prolonged exposure, especially in the presence of folate deficiency, could lead to formate accumulation and subacute impairment of visual function. Furthermore, it should be noted that physiological levels of methanol are present in the blood, from environmental exposure and derived from diet through normal metabolic processes. Methanol and/or formate can be found in some foods, including fruits, vegetables, juices (mainly orange, grapefruit and tomato), fermented beverages, aspartame sweetened foods, beans, honey and roasted coffee.[20]

In order to investigate folate and formate levels in CEN patients, JE traveled to Cuba in 1994 with AS and contacted the INN's Neurochemistry Laboratory, which had stored serum, and CSF samples from CEN-confirmed patients in Pinar del Río. Formate analysis was conducted at INN and samples were transported to the USA for folate analysis. Marked folate deficiency was detected in more than 50% of samples analyzed, and serum formate

Lessons in International Cooperation

accumulation in 25%. Folate concentration was inversely correlated with severity of optic neuropathy, while formate concentration was directly correlated.[21] Although it is unlikely that classic methanol poisoning (which produces an acute formate acidosis) could have significantly contributed to the entire epidemic, consumption of ethylic alcohol containing small amounts of methanol was a risk factor for developing the disease.[5] It should be emphasized that this study included patients from the same region where the home-brewed rum samples had been taken, and 55% were alcohol drinkers; thus chronic formate toxicity may have contributed to triggering the disease in some patients.[22] Gay's Isle of Youth study concluded that smoking and alcohol consumption did not by themselves account for disease occurrence but reinforced the effects of dietary deficiencies.[23]

At this point in the investigation of CEN, the need emerged to develop animal models matching some characteristics of the Cuban patients, especially the possibility of chronic low-level methanol exposure in the presence of folate deficiency. The rationale was to combine folate deficiency with chronic methanol toxicity so as to increase formate production to match serum levels observed in CEN patients. Two models were developed independently by Cuban researchers. One was an experimental model of chronic methanol administration in rats with dietary folate deficiency.[22] Analysis of optic discs disclosed prelaminar axonal swelling anterior to the lamina cribrosa, indicating axoplasmic blockage at this level. Ultrastructural examination revealed early axonal degeneration and a relative abundance of mitochondria, many of which were swollen and with disrupted cristae. These histopathologic features matched very closely those observed in the optic disc of a CEN patient who died of unrelated causes. Due to the selective action of formic acid as an inhibitor of mitochondrial function,[24] these results supported the hypothesis that impaired mitochondrial oxidative phosphorylation produced axoplasmic blockage.

The second model was developed in rats with chronic low-level methanol administration and folate deficiency induced by methotrexate, where accumulation of aspartate (an excitotoxic amino

acid) was detected in the optic nerve.[25] results which paralleled the increased levels of aspartate and glutamate in CEN patients' CSF,[18] suggesting participation of excitotoxic mechanisms.

Pathophysiological mechanisms underlying CEN Very early in the investigation, striking clinical similarities with Leber hereditary optic neuropathy (LHON) were recognized and later discussed with international experts, leading to the search for mutations in patients.[26,27] However, later it was definitively demonstrated that CEN was not associated with LHON.[28] As the main pathogenic mutations of LHON affect subunits of the mitochondrial complex in the respiratory chain, it was suspected that CEN was possibly affecting mitochondria on an acquired basis.[29]

Clinical, epidemiological, neurochemical and experimental studies revealed possible mechanisms underlying CEN, most likely resulting from insults to the mitochondrial oxidative phosphorylation pathway from severe nutritional deficiencies (folic acid and other B-complex vitamins), leading to impaired detoxification mechanisms and thus to chronic accumulation of exogenous and endogenous toxins (formate from methanol metabolism, and/or exposure to cyanide from dietary products and cigarette smoke).[22] Furthermore, in CEN's pathophysiological mechanism, where oxidative stress was definitely the "conductor of the orchestra," three interrelated processes may have been present: excitotoxicity, blood-brain barrier dysfunction and formate toxicity. Additionally, a selective taurine deficiency may have complicated the picture due to its abundance in the retina and well-known antioxidant and neuroprotective properties.[30]

CONCLUSION

Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can work to solve important health problems, in this case, further shedding light on other metabolic or mitochondrial optic neuropathies. US-Cuba cooperation, under the PAHO/WHO umbrella, was key to developing, pursuing and generating evidence to support the nutritional-toxic hypothesis of CEN etiology. 

REFERENCES

1. CNFIT. The Cuban Neuropathy Field Investigation Team. Epidemic optic neuropathy in Cuba—Clinical characterization and risk factors. *NEJM*. 1995 Nov 2;333(18):1176–8.
2. Román GC. An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy. *J Neurol Sci*. 1994 Dec 1;127(1):11–28.
3. CDC. International notes Epidemic Neuropathy – Cuba, 1991–1994. *CDC. MMWR Morb Mortal Wkly Rep*. 1994 Mar 18;43(10):183,189–92.
4. Más P, Pelegrino JL, Guzmán MG, Comellas MM, Resik S, Álvarez M, et al. Viral isolation from cases of epidemic neuropathy in Cuba. *Arch Pathol Lab Med*. 1997 Aug;121(8):825–33.
5. Sadun AA, Martone JF, Muci-Mendoza R, Reyes L, Dubois L, Silva JC, et al. Epidemic optic neuropathy in Cuba. *Eye Findings. Arch Ophthalmol*. 1994 May;112(5):691–9.
6. Lincoff NS, Odel JG, Hirano M. "Outbreak" of optic and peripheral neuropathy in Cuba? *JAMA*. 1993 Jul 28;270(4):511–8.
7. Hedges TR 3rd, Hirano M, Tucker K, Caballero B. Epidemic optic and peripheral neuropathy in Cuba: a unique geopolitical public health problem. *Survey Ophthalmol*. 1997 Jan–Feb;41(4):341–53.
8. Hadad Hadad J. International Workshop on Epidemic Neuropathy in Cuba: Report Summary. *MEDICC Rev* [Internet]. 2005 Jul [cited 2017 Apr 5];7(7). Available from: http://www.medicc.org/publications/medicc_review/0705/cuban-medical-literature-2.html
9. Declaration of Helsinki. 48th World Medical Assembly, Somerset West, Republic of South Africa (Oct. 1996) [Internet]. Ferney-Voltaire: World Medical Association; 1996 Oct [cited 2017 Apr 5]. 3 p. Available from: <https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct1996.pdf>
10. Santiesteban-Freixas R, Márquez M. Características neurofisiológicas y neurofisiológicas de la neuropatía epidémica. In: Hernández A, Antelo Pérez J, Ballester Santovenia J, Borrajero Martínez I, Cabrera Hernández A, Calcagno Tey E, et al, editors. *Neuropatía epidémica en Cuba 1992–1994*. Havana: Editorial Ciencias Médicas; 1995. p. 35–45. Spanish.
11. Santiesteban-Freixas R, Mendoza-Santiesteban CE, Columbie-Garbey Y, González-Quevedo A, González García A, Cabal Rodríguez R. Cuban Epidemic Optic Neuropathy and its relationship to toxic and hereditary optic neuropathy. *Sem Ophthalmol*. 2010 Jul;25(4):112–22.
12. Ishihara S. Tests for color blindness. Tokyo: Major, IJAMC; 1917.
13. Llanos G, Asher D, Brown P, Gajduzek DC, Muci-Mendoza R, Márquez M, et al. Epidemic neuropathy in Cuba. *Epidemiological Bulletin. Pan Amn Health Organization*. 1993;14(2):1–4.
14. Amsler M. L' Examen qualitatif de la fonction maculaire. *Ophthalmologica*. 1947;114:248–61. French.
15. Alfaro I, González-Quevedo A, del Pino M, Serrano C, Lara R, González H, et al. Immunoglobulins in epidemic neuropathy in Cuba. *J Neurol Sci*. 1994 Dec 20;127(2):234–5.
16. González-Quevedo Monteagudo A, Fernández Carriera R, Santiesteban Freixas R, Alfaro Capdegelle I, Lara Rodríguez R, Vicente Valdés I, et al. Brain barrier dysfunction in Cuban Epidemic Optic Neuropathy. *Eur J Neurol*. 2008 Jun;15(6):613–8.
17. Porrata C, Abreu M, Hernández M, Gay J, Hevia G, Márquez H. Asociación de la ingestión de aminoácidos esenciales y la neuropatía epidémica en la Isla de la Juventud. *Rev Cub Aliment Nutr*. 1995;9:16–22. Spanish.
18. González-Quevedo A, Obregón F, Fernández R, Santiesteban R, Serrano C, Lima L. Amino acid levels and ratios in serum and cerebrospinal fluid

- of patients with Optic Neuropathy in Cuba. *Nutr Neurosci*. 2001;4(1):51–62.
19. Lima L. Taurine and its trophic effects in the retina. *Neurochem Res*. 1999;2:1333–8.
 20. World Health Organization. Environmental Health Criteria 196: Methanol [Internet]. Geneva: World Health Organization; 1997 [cited 2018 Apr 9]. Available from: <http://www.inchem.org/documents/ehc/ehc/ehc196.htm>
 21. Eells JT, González-Quevedo A, Santiesteban R, McMartin KE, Sadun AA. Deficiencia de folato y concentraciones elevadas de formato en suero y líquido cefalorraquídeo de pacientes con neuropatía óptica epidémica. *Rev Cubana Med Trop*. 2000 Jan–Apr ;52(1):21–3. Spanish.
 22. Sadun AA. Acquired mitochondrial impairment as a cause of optic nerve disease. *Trans Am Ophthalmol Soc*. 1998;96:881–923.
 23. Gay J, Porrata C, Hernández M, Clua AM, Arguelles JM, Cabrera A, et al. Dietary factors in epidemic neuropathy on the Isle of Youth, Cuba. *Bull Pan Am Health Org*. 1995 Mar;29(1):25–36.
 24. Zerín T, Kim JS, Gil HW, Song HY, Hong SY. Effects of formaldehyde on mitochondrial dysfunction and apoptosis in SK-N-SH neuroblastoma cells. *Cell Biol Toxicol*. 2015 Dec;31(6):261–72.
 25. González-Quevedo A, Obregón F, Urbina M, Roussó T, Lima L. Effect of chronic methanol administration on amino acids and monoamines in retina, optic nerve and brain of the rat. *Toxicol Appl Pharmacol*. 2002 Dec 1;185(2):77–84.
 26. Hirano M, Cleary JM, Stewart AM, Lincoff NS, Odel, JG, Santiesteban R, et al. Mitochondrial DNA mutations in an outbreak of optic neuropathy in Cuba. *Neurology*. 1994;44:843–5.
 27. Johns DR, Neufeld MJ, Hedges TR 3rd . Mitochondrial DNA mutations in Cuban optic and peripheral neuropathy. *J Neuroophthalmol*. 1994 Sep;14(3):135–40.
 28. Newman NJ, Torroni A, Brown MD, Lott MT, Fernández MM, Wallace DC. Epidemic neuropathy in Cuba not associated with mitochondrial DNA mutations found in Leber's hereditary optic neuropathy patients. *Am J Ophthalmol*. 1994 Aug 15;118(2):158–68.
 29. Sadun AA. Mitochondrial optic neuropathies. *J Neurol Neurosurg Psychiatry*. 2002 Apr;72(4):423–5.
 30. González-Quevedo A, Santiesteban Freixas R, Eells JT, Lima L. Cuban Epidemic Optic Neuropathy. An appraisal of the pathophysiological mechanisms. In: Holmgren A, Borg G, editors. *Handbook of Disease Outbreaks: Prevention, Detection and Control*. New York: Nova Science Publishers; 2010. p. 43–73.
- Full professor and senior researcher, Neuro-ophthalmology Department, Neurology and Neurosurgery Institute, Havana, Cuba.
- Janis T. Eells**, pharmacologist with a doctorate in pharmacology and toxicology. Distinguished Professor, College of Health Sciences, University of Wisconsin–Milwaukee, USA.
- Lucimey Lima**, psychiatrist and neurochemist. Senior researcher. Neurochemistry Laboratory. Venezuelan Institute of Scientific Research, Caracas, Venezuela.
- Alfredo A. Sadun**, neuro-ophthalmologist. Flora L. Thornton Chair, Doheny Eye Centers, University of California at Los Angeles (UCLA) and Vice-Chair of Ophthalmology UCLA School of Medicine, Los Angeles, USA.

THE AUTHORS

Alina González-Quevedo Monteagudo (Corresponding author: aglez@infomed.sld.cu), physician specializing in clinical biochemistry with a doctorate in medical sciences. Full professor and senior researcher, Neurobiology Laboratory, Neurology and Neurosurgery Institute, Havana, Cuba.

Rosaris Santiesteban-Freixas, ophthalmologist with a doctorate in medical sciences.

Submitted: October 30, 2017

Approved for publication: March 13, 2018

Disclosures: None



4th International Congress on
Research, Development and Innovation
in the Biopharmaceutical Industry

IDIFARMA 2018

December 3–7, 2018
Havana's International Convention Center

Main topics:

- Research, development and innovation
- Pharmaceutical technology
- Pharmacology and toxicology
- Environmental management in the biotech and pharmaceutical industries
- Quality management and control systems
- Pharmaceutical regulations
- Industrial property
- Negotiations and investments
- Commercialization and marketing
- Human resources management

Information: mireya@palco.cu <http://www.idifarmacuba.com/es/invitation>

ERRATA

Chapman HJ, Armas-Pérez LA, Lauzardo M, González-Ochoa ER. Moving Closer to Tuberculosis Elimination through Institutional Scientific Collaboration: Opportunities for Cuba and the USA. *MEDICC Rev.* 2018;20(2):59–63.

Page 60, Table 1, rows 9 and 10: row labels “New cases (%)” and “Previously treated cases (%)” should be indented, to make clear that they are subsets of MDR-TB cases.

González-Quevedo A, Santiesteban-Freixas R, Eells JT, Lima L Sadun AA. Cuban Epidemic Neuropathy: Insights into the Toxic–Nutritional Hypothesis through International Collaboration. *MEDICC Rev.* 2018 Apr;20(2):27–31.

Page 30, first complete paragraph, line 7, “Two models were developed independently by Cuban researchers” should read “Two models were developed independently by AAS and AGQ.”