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Pugwash Conferences on Science and World Affairs

In 1995, the Pugwash Conferences and one of its cofounders, the physicist Sir Joseph Rotblat, shared the Nobel Peace Prize in recognition of their decades-long work to reduce the threat of nuclear war and ultimately abolish nuclear and other weapons of mass destruction. Beginning with its first international conference in Pugwash, Nova Scotia in 1957, the Pugwash Conferences have brought together influential scientists, scholars and public figures concerned with reducing the danger of armed conflict and seeking cooperative solutions for global problems.

Today, there are some 50 national Pugwash groups around the world, and four offices in Cambridge, Mass., Rome, London, and Geneva. The current President of Pugwash is Sir Michael Atiyah (former President of the Royal Society in the UK); the Secretary General is Prof. George Rathjens (Professor Emeritus of the Massachusetts Institute of Technology); Prof. Francesco Calogero (Professor of Theoretical Physics at the University of Rome, La Sapienza) is Chair of the Pugwash Council; and Prof. Ana María Cetto (Prof. of Physics at the National University of Mexico) is chair of the Pugwash Executive Committee.

Stimulated by the Russell-Einstein Manifesto of 1955, and founded on the principle of the individual responsibility of scientists for their work, the Pugwash Conferences have worked for 45 years toward the twin goals of abolishing nuclear weapons and the peaceful settlement of international disputes. The emerging challenges in science, technology and international politics of the 21st century make those principles and goals more relevant than ever.

Pugwash

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With this inaugural issue of the ***Pugwash Policy Brief*** series, the Pugwash Conferences are initiating a new series of publications aimed at highlighting important issues which lie at the intersection of science, technology and public policy.

Intended for wide circulation to policy makers and analysts, the media, NGOs, the academic and research communities, as well as the Pugwash community, the ***Pugwash Policy Briefs*** will contain articles, commentaries and conclusions that emanate from the broad range of Pugwash workshops and conferences held each year. Perspectives and recommendations contained in the ***Policy Briefs*** represent those of individual authors and workshop rapporteurs, not of the Pugwash Conferences or its funders. ***Pugwash Policy Briefs*** are funded in part by the John D. and Catherine T. MacArthur Foundation.

Pugwash

POLICY BRIEF

Issued by the Council of the Pugwash Conferences on Science and World Affairs
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US-Cuban Medical Cooperation: Effects of the US Embargo

This ***Pugwash Policy Brief*** examines some consequences of the 40-year US economic embargo of Cuba, not only for the health and welfare of the Cuban people, but for constraining potential medical advances and the availability of treatments and medicines that could benefit Americans and others around the world. It is the result of a Pugwash Conferences workshop on *Medical Research in Cuba: Strengthening International Cooperation*, that took place from 15-17 February 2001 in Havana, Cuba. More than 30 participants from seven countries attended the workshop, which was hosted by the Cuban Pugwash Group. Participants at the workshop shared current research in such areas as cancer therapy, development of vaccines for hepatitis-B and meningitis, and sickle cell anemia.

One of the papers presented at the workshop (subsequently revised and included here), by Kenneth D. Bridges, M.D., of Brigham and Women's Hospital in Boston, focused in particular on the constraints faced by US physicians and medical researchers in not being able, because of the US embargo, to fully cooperate with Cuban colleagues working on sickle cell anemia research and treatments in Cuba. As pointed out in the paper by Dr. Bridges and in the Pugwash workshop report, sickle cell anemia research is but one of many examples of the embargo's consequences for the health and well-being of Americans and others around the world who could benefit from Cuban development of medical vaccines and treatments.

Despite the twin constraints of a developing country economy and the US embargo, the Cuban medical research community and public health care system have much to offer both their immediate neighbors and the wider international community. Conflicting views on the embargo and Cuba's political system notwithstanding, international NGOs such as Pugwash have a responsibility to facilitate the free and open exchange of information and research between the Cuban scientific and medical community and their international colleagues.

For more on the Pugwash workshop held in Havana in February 2001, visit the Pugwash website at www.pugwash.org

> **"Public health and medicine are social interventions, and politics are public health in the most profound sense."**
>
> **— Rudolf Virchow (1821-1902)**

Sickle Cell Disease in Cuba and the US: Effects of the Economic Embargo

by Kenneth R. Bridges, M.D.

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The United States has maintained an economic embargo of Cuba for 40 years, despite dramatic changes in the world's geopolitical landscape. In 1972, President Richard Nixon opened the door to mainland China, and the US now has a brisk and growing trade relationship with the world's sole remaining major communist economic and military power. In the late 1980s, the collapse of the Soviet Union and the disintegration of the Warsaw Pact transformed the economic and strategic face of Europe. In the 1990s, Poland, Hungary and the Czech Republic joined NATO as democratic states, and more former communist countries may follow suit.

The Cuban economic embargo is a relic of a world that exists now only as a specter in the nightmares of aging anachronistic Cold Warriors. More than ever in today's globalizing world, an examination of the biomedical impact of the embargo is long overdue. Illness, injury and suffering, unlike political dogma, could care less about national boundaries. Sickle cell disease is a scourge both in the United States and Cuba, and the embargo has injured people suffering from the disease in both nations.

An Overview of Sickle Cell Disease

Sickle cell disease results from a mutation in the b-globin gene that substitutes a valine residue for glutamic acid at position 6. This single alteration profoundly changes the biophysical properties of the hemoglobin molecule. Hemoglobin (inside red blood cells) picks up oxygen in the lungs and releases it to the peripheral tissues. Normal and sickle hemoglobin bind and release oxygen identically.

The key difference between the two molecules is their behavior after oxygen is released. Deoxygenated normal hemoglobin retains its solitary existence in the red cell. In contrast, deoxygenated sickle hemoglobin molecules adhere to form long chains or polymers. The molecules in the polymers dissociate when the red cells return to the lungs and pick up oxygen. The sickle hemoglobin polymers form stiff rods that stretch and distort the red cells. These distorted cells can obstruct blood flow through the small vessels in the tissues. The restricted oxygen delivery to the tissues damages cells, injures organs and produces pain.

Pain is the primary manifestation of sickle cell disease. The disorder varies tremendously in severity. Some people have only occasional pain episodes that require nothing stronger than over-the-counter pain relievers. Other people experience pain of such severity and frequency that only powerful, long-acting narcotic analgesics provide relief.

Poor tissue oxygenation damages organs. Sickle cell disease can injure every organ in the body. Strokes, bone degeneration, chronic leg ulcers and kidney failure are a few of the many problems that can follow in the wake of sickle cell disease. Sickle cell disease begins to produce

problems in the first six to twelve months of life. The condition often waxes and wanes in severity over the course of a person's life. Fixed organ injury often manifests in adults due to accumulating cell damage.

World Distribution of Sickle Cell Disease

The sickle gene mutation arose in tropical areas of the old world as a defense against malaria. People with one sickle gene and one normal gene (sickle cell trait) suffer none of the ill effects seen with sickle cell disease (two sickle genes). People with sickle cell trait are more resistant to malaria, on average, than are people who have two normal hemoglobin genes. People with two sickle cell genes were likely to die of sickle cell disease. People with two normal genes were likely to fall victim of malaria. People with sickle cell trait survived and passed their genes (both normal and sickle) on to the next generation. The incidence of sickle cell trait reaches levels of 30 to 40 percent in equatorial Africa and India. The sickle gene arose independently in these two regions of the world.

Sickle cell disease in the Americas largely reflects the African slave trade. People captured in Africa were transported to the New World, with the Caribbean islands serving as the initial triage point. These islands retained some people to work in the burgeoning sugarcane industry. Others were transported to continental slave markets, including those in North America. A person suffering from sickle cell disease lives in Cuba or the United States solely by luck-of-the-draw of long-forgotten ancestors.

Advances in the Management of Sickle Cell Disease

Sickle cell disease first appeared in the medical literature in 1910 in a report by Herrick.[1] In 1956, Ingram and colleagues at the MRC in Cambridge, UK defined the mutation in the hemoglobin molecule responsible for sickle cell disease.[2] Despite detailed knowledge of the mutation that produces sickle hemoglobin, no cure exists. Nonetheless, significant advances in the management of sickle cell disease have been made over the past 15 years.

Sickle Cell Anemia in Cuba

Ethnic composition of the Cuban population (11,150,000):

Mulatto	51 %
White	37 %
Black	11%
Chinese	1%

Incidence of sickle cell trait

General population	3.08%
Whites	0.6%
Blacks	13.2%
Eastern provinces	5.59–10.6 %
Western provinces	2.12–3.04 %

Source: Dr. Eva Svarch, Dr. Porfirio Hernández, Dr. José Manuel Ballestero Instituto de Hematología e Inmunología (IHI), La Habana, Cuba

Early childhood mortality from overwhelming infection is a major risk for children with sickle cell disease. A study sponsored by the US National Institutes of Health showed unequivocally in 1986 that daily treatment with penicillin (called prophylaxis) dramatically lowers this risk.[3] The data from the study were so compelling that the study was curtailed early with the recommendation that all infants and young children be placed on penicillin prophylaxis.

A second major advance was the introduction of hydroxyurea to treat people with very severe sickle cell disease. A randomized, controlled multicenter study of hydroxyurea in sickle cell anemia was terminated earlier than planned when the drug prevented severe problems including pain crises and a particularly deadly complication called "acute chest syndrome".[4] Patients respond variably to hydroxyurea and some derive no benefit at all. Perhaps 25 percent of patients improve dramatically with hydroxyurea, some almost miraculously so. Hydroxyurea is now an essential part of the treatment armamentarium for sickle cell disease.

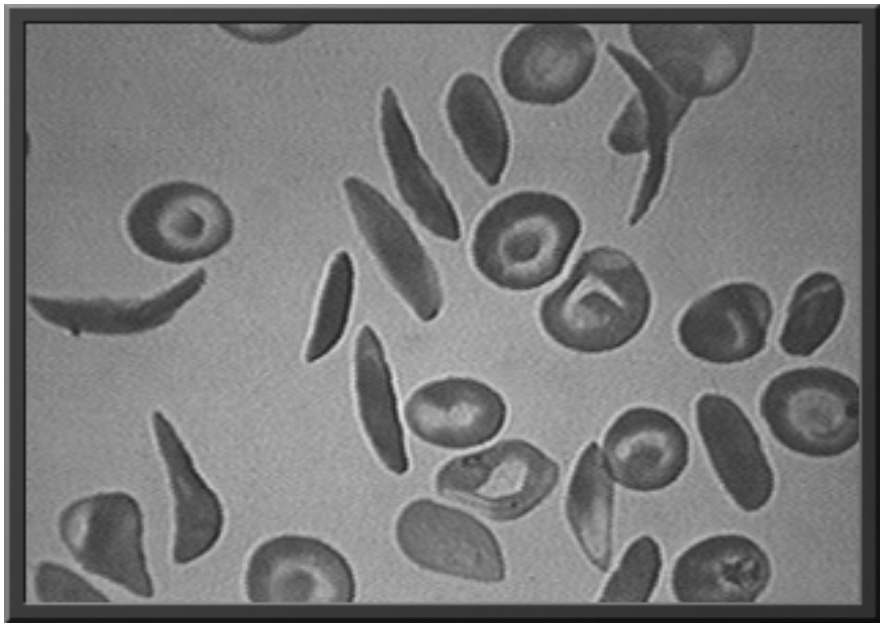
A number of other interventions have improved the clinical outlook and quality of life for patients with sickle cell disease. A number of additional therapies are currently being investigated. As a result, the next five to ten years hold great promise for patients with sickle cell disease and their families.

[1] Herrick, JB 1910. Peculiar elongated and sickle shaped red blood corpuscles in a case of sever anemia. Arch. Int. Med. 6: 517-527.

[2] Ingram, V.M. (1956) A specific chemical difference between globins of normal and sickle-cell anœmia hœmoglobins. Nature 178, 792-794.

[3] Gaston MH, Verter JI, Woods G, et al. 1986. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 314: 1593-1599.

[4] Charache S, et al. 1995. Effect of hydroxyurea on the freqency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N. Engl. J. Med. 322:1317.



Microscopic view of sickle cells

The Embargo and Sickle Cell Disease

Cuba has a newborn screening program to identify all infants with sickle cell disease. A program of prophylactic penicillin currently exists. The US economic embargo has produced shortages of drugs at times, including antibiotics. Fortunately, these shortages have not disrupted the prophylactic penicillin program. This program, along with other health measures, has substantially reduced the incidence of childhood mortality from sickle cell disease among Cuban children.

Patients with more clinically severe sickle cell disease are treated with hydroxyurea. A cohort of Latin American countries recently instituted a multinational study of hydroxyurea in children with sickle cell disease. Cuban investigators are leading this effort because of their extensive experience in conducting clinical trials. The National Institutes of Health in the US recently conducted a trial of hydroxyurea in children (HUG Study) that demonstrated the short-term safety of this drug. This agency is poised to begin another study, this one examining hydroxyurea in infants six months of age and older.

Both penicillin and hydroxyurea are generic drugs, making them easier for Cuban physicians to acquire. Penicillin is relatively inexpensive. Hydroxyurea is not. The economic embargo strains the Cuban economy such that the availability of hydroxyurea is suboptimal.

For the first time, several drugs and interventions for patients with sickle cell disease are being investigated. These include clotrimazole, nitric oxide, Fluocor™ and non-ablative bone marrow transplantation. Not all these approaches will prove to be clinically useful in the treatment of sickle cell disease. Cuban patients suffering from sickle cell disease may not have access to interventions and drugs that are efficacious due to the economic embargo. The economic embargo promotes unwarranted suffering and even death due to the restrictions in access to medical care.

The economic embargo also injures people in the US afflicted with sickle cell disease. Approximately 70,000 Americans suffer from sickle cell disease. Most are not followed at comprehensive medical centers that perform clinical trials. Neither a registry nor a clinical trials network exists in the US. The National Institutes of Health funds ten Comprehensive Sickle Cell Centers. For a variety of reasons these centers have given clinical trials a low priority. Slow patient accrual has limited the pace of clinical trials in the US.

Cuba has a well-established patient care network. Excellent facilities for patient trials exist both in Havana and Santiago de Cuba. Cuba has a registry of patients with sickle cell disease, which is a valuable tool in clinical investigation. Lifting the economic embargo, at least as it applies to medical care, would allow American and Cuban physicians to work together on the problems of sickle cell disease. Thirteen percent of Cubans of African descent have sickle cell trait. The incidence is highest in the eastern provinces where 6-11 percent of *all* Cubans have sickle cell trait. Patients with sickle cell disease in these regions alone would significantly expand the number of people enrolled in multinational trials. Enrollment of patients in joint research protocols would speed the process of identifying useful interventions for sickle cell disease. Lifting the embargo would greatly benefit a most vulnerable group of Americans with a debilitating and often deadly disease.

Useful Websites:

Joint Center for Sickle Cell and Thalassemic Disorders
http://sickle.bwh.harvard.edu

Emory University Sickle Cell Disease Center
http://www.emory.edu:80/PEDS/SICKLE

Pugwash Meeting no. 259

Medical Research in Cuba: Strengthening International Cooperation

Infectious Diseases and Vaccination Programs: The Cuban Experience

Cuba has a long and successful tradition of dealing with infectious diseases, being the first country in the world to eradicate smallpox (1923) and polio (1962). Other diseases which were endemic but which have all been eradicated include cholera, yellow fever, bubonic plague, malaria, diphtheria, measles, rubella, and mumps. Other diseases such as meningeal tuberculosis, whooping cough and tetanus have been reduced to levels of around one case per 10,000 inhabitants. Despite being a developing country, Cuba has been so successful in reducing the incidence of infectious disease that the main causes of mortality in the country today (as in the US and other developed countries) are heart disease and cancer, leading many Cubans to joke that "we live as poor people, but we die like rich people." Indeed, Cuba compares favorably with many developed countries across a broad range of public health indicators, having been ranked 39 out of 191 countries in a 2000 report by the World Health Organization.

Having inaugurated its National Immunization Program in 1962, Cuba today is one of very few countries in the world to vaccinate 100 percent of its population against 12 different diseases. In other low income countries, by comparison, 45 percent of all deaths (63 percent for children) are due to infectious diseases, with the most deadly being Acute Respiratory Infection, AIDS, diarrhea, TB, and malaria. As Cuba has shown, many of these deaths could be prevented through a combination of widespread vaccinations using cost-effective medicines via a public health system that covers the entire country.

Medical and Biotechnology Research in Cuba

Beginning with the creation in 1965 of the Center for Scientific Investigation, biotechnology and medical research have been top priorities of the Cuban government. There are today some 38 biotech and medical research centers, grouped together in a science park to the west of Havana, which in the 1990s were supported with over one billion dollars of government R&D investment. Through the integration of research, development, production and marketing, Cuba has implemented a highly focused strategy that has enabled the country to eradicate numerous diseases and to control epidemics in remarkably short periods of time.

With over 400 patents in the biotech field, Cuba's research community has produced a variety of products ranging from vaccines and

The following are excerpts from the rapporteur's report by Amina Aitsiselmi, Pugwash Newsletter, *June 2001*

Pugwash Workshop #259 on Medical Research in Cuba took place 15–17 February 2001, in Havana, Cuba

Center for Genetic Engineering and Biotechnology

cancer therapy drugs to fetal monitoring equipment. Some of the many examples include:

- Monoclonal antibody and interferon, for the treatment of cancer and viral diseases;
- Anti-meningitis B and hepatitis B vaccine, both have been certified by the WHO;
- Recombinant streptokinase for the treatment of heart attacks;
- biomodulin-T;
- blood derivatives (albumin, anti-meningococcal immunoglobulin);
- vaccines (rabies, small pox, tetanus, diphtheria; salmonella tiphi).

Cuba also has several products in the pipeline, including: combined vaccines, cholera vaccine, cancer vaccines; an AIDS vaccine; new radioactive mabs, interleukin-2, and new interferon combinations, all currently undergoing clinical trials. At present, Cuba exports its products to over 20 countries, including the UK and Canada, but not, course, the United States.

According to the CIA, Cuba has a life expectancy rate of 76.21 years, an infant mortality rate of 7.51 per thousand, and a literacy rate of 95.7 percent, all comparing very favorably with many of the world's wealthier nations; see *The World Factbook 2000* (Washington, DC: Central Intelligence Agency, 2000)

Impact of the US Embargo

In place since the early 1960s, the US embargo against Cuba is the only embargo in recent history that has explicitly *included* food and medicine, compared even with international embargoes against Iraq and North Korea (two countries that, unlike Cuba, are suspected of developing nuclear weapons). In so doing, US policy is in direct violation of Article 4 of the Geneva Convention, Article 12 of the UN Charter on Human Rights and various other international human rights accords.

Prior to the 1990s, Cuba was able to minimize the impact of the US blockade by purchasing drugs in both western and eastern Europe. Following the collapse of the Soviet Union, however, East European supplies as well as the hard currency to purchase drugs in Western Europe dried up.

Cuba has responded to these shortages through a combination of rationing, import substitution and domestic production of drugs and pharmaceuticals. For example, the National Medicines Program has been forced to tightly control prescriptions, by banning drug dispensing from hospitals and by restricting the affiliations of physicians to only one pharmacy. In addition, while import substitution tactics have saved millions of dollars, Cuba nonetheless had to implement a VEN (Vital, Essential and Non-essential) system of drug classification. Even with such measures, such basic medicines as Ibuprofen, Vitamin E and Erythromycin are not available in the country.

Moreover, the 1990s witnessed a period of smaller European pharmaceutical companies being bought up by US companies, thus coming under the terms of the embargo. This situation was further compounded by implementation of the so-called "Cuban Democracy Act" of 1992 and its effect on food and medicines, including:

- a ban on subsidiary trade, where European companies that are subsidiaries of US companies may no longer sell to Cuba;
- a licensing provision permitting the sale of drugs for humanitarian reasons which was so arduous and protracted it had no practical benefit;
- the prohibition on foreign ships docking in the US if they have visited Cuba in the previous six months;

In looking at just one of these provisions, the prohibition on foreign ships docking in the US, Cuba pays substantial shipping costs for imported materials because of the economic inefficiencies of foreign ships not being able to travel on to the US after having visited Cuba. In part because of this, imported pharmaceuticals soak up around 52 percent of Cuba's total public health expenditure.

The passage of the Helms-Burton Act in 1996 further tightened restrictions in that various components of the embargo could only be changed by an act of Congress rather than by executive order. This legislation was especially damaging as it also targeted the biotechnology sector, which had proven such a success scientifically and financially for Cuba.

In 1997, the American Association for World Health (AAWH) published a comprehensive study of the impact of the embargo on the health of the Cuban people* (an updated review by AAWH is planned for 2002). This document provided hard data for those seeking to exclude food and medicine from the embargo, including:

- a widespread shortage of nearly all pharmaceuticals (only 889 of the 1297 medications previously available in 1991 were still available, and some of these only intermittently);

- a degradation of the island's water supply due to a lack of access to water treatment chemicals and spare parts, which resulted in a rise in mortality and morbidity;
- serious nutritional deficits, particularly among pregnant women, due to the ban on foodstuffs;
- constraints on the exchange of information due to travel restrictions, currency regulations, etc. Although information materials are theoretically exempt from the embargo, scientists and citizens of Cuba, the US and other countries suffer as a result.

One of the unintended benefits of the embargo for Cuba is that the country has developed a remarkable self-reliance in terms of both health care and biotechnology. Given severe resource constraints, Cuba has emphasized the fundamentals of medical practice (physical diagnosis and clinical judgment) and the implementation of a model public health care system. Despite these achievements, however, the fundamental violations of international law and human rights imposed by the US embargo remain unchanged.

For more information on Cuban medical and biotechnology research, see *Biotechnology in Cuba: A Report on A Scientific Mission to Cuba*, American Association for the Advancement of Science (Washington, DC: AAAS, 1998).

* *See "Denial of Food and Medicine: The Impact of the US Embargo on Health and Nutrition in Cuba," American Association for World Health (Washington, DC; March 1997).*