The centennial of the Yellow Fever Commission and the use of informed consent in medical research

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Abstract
The year 2000 marked the centennial of the discovery of the mode of transmission of yellow fever. Informed consent was systematically used for the first time in research. This process was the result of a complex social phenomenon involving the American Public Health Association, the US and Spanish Governments, American and Cuban scientists, the media, and civilian and military volunteers. The public health and medical communities face the AIDS pandemic at the beginning of the 21st Century, as they faced the yellow fever epidemic at the beginning of the 20th Century. Current medical research dilemmas have fueled the debate about the ethical conduct of research in human subjects. The AIDS pandemic is imposing enormous new ethical challenges on the conduct of medical research, especially in the developing world. Reflecting on the yellow fever experiments of 1900, lessons can be learned and applied to the current ethical challenges faced by the international public health research community.

Key words: yellow fever; informed consent; research; ethics, medical

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At the start of the 21st Century, the medical research community in the United States is engaged in multiple controversies and debates regarding the ethical conduct of research in human subjects. Examples of these controversies include the use of certain methods in the conduct of researching poor and minority populations, and the application of new medical technologies such as gene therapy. Clinical trials being conducted in leading academic medical research centers in the United States have been ordered to temporarily stop because of alleged violations in the safe implementation of the approved protocols.

This array of new challenges has resulted in the establishment of a new government agency for ethics in medical research, led by an "Ethics Czar." The global public health community is facing the deadly AIDS pandemic at the beginning of the 21st Century, as it faced yellow fever at the beginning of the 20th Century. The AIDS pandemic is imposing enormous new ethical challenges, especially on the conduct of medical research in the developing world. Recently published scientific papers from research conducted in the countries most affected by the AIDS pandemic, are putting into question the principles of social justice and the distribution of benefits derived from medical research. The Declaration of Helsinki was under revision because of these new ethical challenges and was modified in October 2000. The public health and research communities have faced and overcome similar challenges in the past.

A milestone in the evolution of ethics in medical research that occurred a century ago, was the systematic use of informed consent during the conduct of research in human subjects. The year 2000 marked the centennial of the discovery of the mode of transmission of yellow fever by the mosquito *Aedes aegypti* (*Culex fasciatus, Stegomyia fasciata*). Recurrent epidemics of yellow fever in the Temperate Zone of North America were responsible for more that 100,000 deaths between the end of the 19th Century and the end of the 19th Century. The American Public Health Association (APHA), which included more than 1,000 members and the sanitary authorities and health officials of the United States, Canada, and Mexico in the 1890's, played a crucial role in this historic episode. Dr. Benjamin Lee, the future chairman of the 29th Annual Meeting of the APHA, presented during the 17th meeting in Brooklyn, New York, in 1899, a "demand for the annexation of Cuba" to sanitize the island. Major William Crawford Gorgas, the sanitary officer in Cuba during the yellow fever experiments, and future Surgeon General of the Army, expressed in 1907 that "Cuba is so situated commercially with regard to our gulf coast that, as long as she was infected with the yellow fever, she was a constant menace to our gulf states, and to the United States generally." The APHA presented draft legislation to William McKinley, President of the United States, requesting the formation of a scientific commission to "study the etiology of yellow fever" in 1897, and because no action was taken by congress, it was presented again in 1898, the year the Spanish-American war began. The result of the war with Spain gave control of Cuba to the United States in 1899, permitting the direct intervention of the United States Army in the investigation of the cause of yellow fever. The Army Board of medical officers, known as the "Yellow Fever Commission", was appointed by George M. Sternberg, Surgeon General of the Army, member of the APHA, and of the Yellow Fever Committee selected by the APHA in 1897. The Yellow Fever Commission, led by Major Walter Reed of the U.S. Army, conducted the classic experiments that proved the hypothesis of the Cuban scientist Dr. Juan Carlos Finlay y Barres, which stated that yellow fever was transmitted by mosquitoes. Dr. Finlay was elected President of the 31st Meeting of the APHA in 1904, and honored during the 32nd Meeting of the APHA in recognition of his scientific work in yellow fever. Major William Crawford Gorgas promptly put science into practice. The sanitary methods in vector control derived from the Yellow Fever Commission’s discovery nearly eradicated the mosquitoes carrying yellow fever from Havana, Cuba. The lessons in sanitation learned in Cuba were then implemented in Panama, successfully controlling the transmission of yellow fever and malaria. Control of yellow fever and malaria allowed the Americans to complete the Panama Canal by 1914, after more than 20 years of unsuccessful efforts by France, and more than 20,000 deaths. This monumental engineering endeavor led to the emergence of the United States of America as a world power.

The Yellow Fever Commission had a less conspicuous achievement of enormous implications for the future of ethics in medical research—the recruitment of informed volunteers through a covenant, a "written informed consent". This approach contrasted with the then prevalent authoritarian methods, absolutely unethical by modern standards, of experimentation in human subjects. This novel research tool was, however, the product of a complex social phenomenon. In November 21st, 1900, the Cuban newspapers aggressively opposed the use of recent Spanish immigrants, who were susceptible to yellow fever, as "Guinea pigs". Brigadier General Leonard Wood, the Military Governor of Cuba, a physician himself, and the Yellow Fever
FIGURE 1. INFORMED CONSENT, IN SPANISH AND ENGLISH LANGUAGES, SIGNED BY THE SPANISH VOLUNTEER ANTONIO BENIGNO IN NOVEMBER 26, 1900. REEVE 41388, OTIS HISTORICAL ARCHIVES, NATIONAL MUSEUM OF HEALTH AND MEDICINE, ARMED FORCES INSTITUTE OF PATHOLOGY, WASHINGTON, D.C.
History of informed consent

In summary, the accomplishments of the Yellow Fever Commission were the result of the application of principles that make a public health intervention successful. The organized political pressure from the APHA made the U.S. Government to take action against the threat that yellow fever posed to the nation and the rest of the American continent. Rather than authoritarian methods, the leadership of the military members of the Commission consulted with the local authorities and built consensus among the native and Spanish immigrant populations of Cuba and sought their cooperation. The subjects who participated in the study were treated ethically, and finally, aggressive implementation of public health measures followed the results of the practice of sound science. The lessons learned from this historic episode can be applied to the current challenges faced by the public health and research communities.

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144

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