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

Fernando Güereña-Burgueño, MD, MPH.(1)

Güereña-Burgueño F.
The centennial of the Yellow Fever Commission and the use of informed consent in medical research.
Salud Publica Mex 2002;44:140-144.
The English version of this paper is available too at: http://www.insp.mx/salud/index.html

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. The English version of this paper is available too at: http://www.insp.mx/salud/index.html

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

Güereña-Burgueño F.
El centenario de la Comisión de la Fiebre Amarilla y el uso del consentimiento informado en la investigación médica.
Salud Publica Mex 2002;44:140-144.
El texto completo en inglés de este artículo también está disponible en: http://www.insp.mx/salud/index.html

Resumen

En el año 2000 se cumplió el primer centenario del descubrimiento del modo de transmisión de la fiebre amarilla. El consentimiento informado fue utilizado por primera vez de manera sistemática en una investigación médica. Este proceso fue el resultado de un fenómeno social complejo que involucró a la Asociación Americana de Salud Pública, a los gobiernos de los Estados Unidos de América y España, a científicos norteamericanos y cubanos, a la prensa y a voluntarios civiles y militares. Al inicio del siglo XXI las comunidades de salud pública y médicas en el ámbito internacional enfrentan la pandemia de SIDA al igual que enfrentaron a la fiebre amarilla al iniciarse el siglo XX. A la vez, también debaten los retos éticos que la investigación médica contemporánea les ofrece, especialmente en los países en desarrollo. La reflexión sobre los experimentos de 1900 podría ofrecer enseñanzas aplicables a los retos éticos enfrentados por las comunidades internacionales de investigación en salud pública. El texto completo en inglés de este artículo también está disponible en: http://www.insp.mx/salud/index.html

Palabras clave: fiebre amarilla; consentimiento informado; investigación; ética médica

The opinions and assertions contained herein are the private ones of the authors and are not to be constructed as official or as reflecting the views of the Department of Defense, or Army.

(1) Walter Reed Army Institute of Research, Division of Communicable Diseases and Immunology, Department of Enteric Infections. United States of America.

Received on: June 4, 2001 • **Accepted on**: October 1, 2001
Address reprint requests to: Fernando Güereña-Burgueño. Walter Reed Army Institute of Research, Division of Communicable Diseases and Immunology, Department of Enteric Infections. 503 Robert Grant Ave. Silver Spring MD, 20910-7500. United States of America.
E-mail: Fernando.Guerena@na.amedd.army.mil

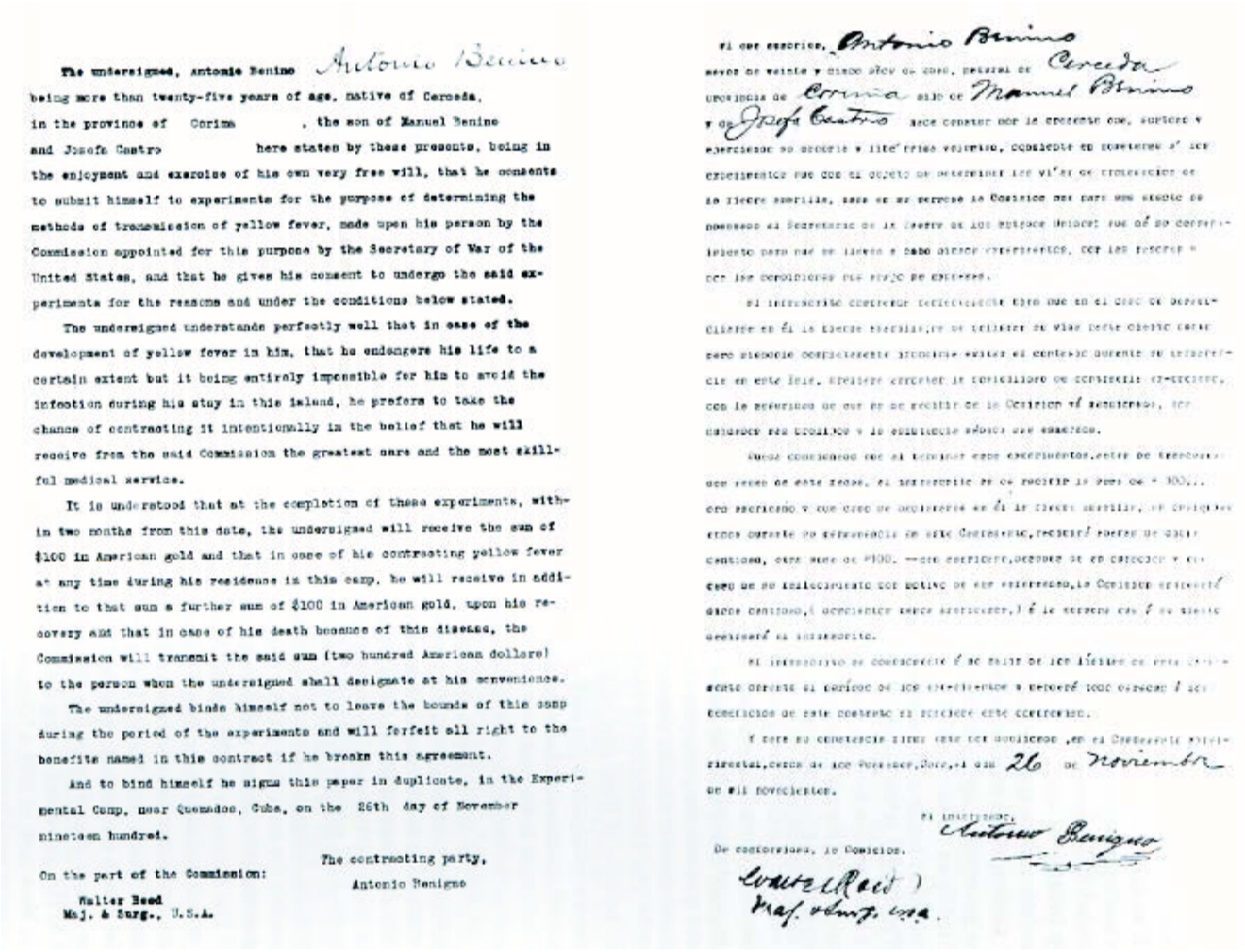
At the start of the 21st Century, the medical research community in the United States is engaged in multiple controversies and debates regarding the ethical conduct of research in human subjects. Examples of these controversies include the use of certain methods in the conduct of researching poor and minority populations,[1,2] and the application of new medical technologies such as gene therapy.[3] 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.[4] This array of new challenges has resulted in the establishment of a new government agency for ethics in medical research,[5] led by an "Ethics Czar".[6]

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.[7-9] The Declaration of Helsinki was under revision because of these new ethical challenges,[10,11] 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, Stegomya 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 18th Century and the end of the 19th Century.[12] 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.[13] 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".[14]

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,[13] 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,[15] 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.[13] The Yellow Fever Commission, led my Major Walter Reed of the U.S. Army, conducted the classic experiments[16,17] 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.[18,19] 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.[20] The lessons in sanitation learned in Cuba were then implemented in Panamá, successfully controlling the transmission of yellow fever and malaria.[14] 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.[21] 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



The undersigned, Antonio Benino Antonio Benino
being more than twenty-five years of age, native of Cerveda,
in the province of Corima , the son of Manuel Benino
and Josefa Castro here states by these presents, being in
the enjoyment and exercise of his own very free will, that he consents
to submit himself to experiments for the purpose of determining the
methods of transmission of yellow fever, made upon his person by the
Commission appointed for this purpose by the Secretary of War of the
United States, and that he gives his consent to undergo the said ex-
periments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the
development of yellow fever in him, that he endangers his life to a
certain extent but it being entirely impossible for him to avoid the
infection during his stay in this island, he prefers to take the
chance of contracting it intentionally in the belief that he will
receive from the said Commission the greatest care and the most skill-
ful medical service.

It is understood that at the completion of these experiments, with-
in two months from this date, the undersigned will receive the sum of
$100 in American gold and that in case of his contracting yellow fever
at any time during his residence in this camp, he will receive in addi-
tion to that sum a further sum of $100 in American gold, upon his re-
covery and that in case of his death because of this disease, the
Commission will transmit the said sum (two hundred American dollars)
to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp
during the period of the experiments and will forfeit all right to the
benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experi-
mental Camp, near Quemados, Cuba, on the 26th day of November
nineteen hundred.

The contracting party,
Antonio Benigno

On the part of the Commission:
Walter Reed
Maj. & Surg., U.S.A.

Yo por escrito, Antonio Benino
mayor de veinte y cinco años de edad, natural de Cereda
provincia de Corima hijo de Manuel Benino
y de Josefa Castro hace constar por la presente que, sujetos a
experimentos que con el objeto de determinar los vías de trasmisión de
la fiebre amarilla, hace de su persona la Comisión nombrada para ese objeto
nombrada al Secretario de la Guerra de los Estados Unidos, fue de su conformidad
dispuesto para que se lleven a cabo dichos experimentos, con las prescripciones
con las condiciones que luego se expresan.

El interesado comprende perfectamente bien que en el caso de desarrollarse en él la fiebre amarilla, por lo mismo que pone en peligro su vida hasta cierto punto pero siendo completamente imposible evitar el contagio durante su estancia en esta Isla, prefiere contraer la enfermedad voluntariamente, con la esperanza de que por de recibir de la Comisión el mejor cuidado, los cuidados más diligentes y la asistencia médica más esmerada.

Queda convenido que al terminar estos experimentos, dentro de dos meses de esta fecha, el interesado se le recibirá la suma de $ 100... oro americano y que caso de contraer en él la fiebre amarilla, en cualquier tiempo durante su residencia en este Campamento, recibirá además de dicha cantidad, otra suma de $100. -- oro americano, después de su curación y en caso de su fallecimiento por motivo de esa enfermedad, la Comisión entregará dicha cantidad, (doscientos pesos americanos,) á la persona que el interesado designará oportunamente.

El interesado se compromete á no salir de los límites de este campamento durante el período de los experimentos y perderá todo derecho á los beneficios de este contrato si rompiere este convenio.

Y para su constancia firma este documento por duplicado, en el Campamento Experimental, cerca de los Quemados, Cuba, el día 26 de Noviembre de mil novecientos.

El interesado,
Antonio Benigno

De conformidad, la Comisión.
Walter Reed
Maj. y Cirujano, U.S.A.

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.

Commission sought the collaboration of the Spanish Consul in Cuba, and turned the public opinion in favor of the investigations.[22] Brigadier General Leonard Wood granted $5 000 to Major Walter Reed "for the purpose of hiring men to submit to these experiments and to the bite of the mosquito on condition that the men should be appraised of their danger and sign papers to that effect; that it should be their own free will in every particular, and that, incase of Spaniards, the Spanish consul's permission should be obtained".[23] The Yellow Fever Commission produced a written document, in Spanish and English, with all the pertinent information about the known benefits and risks to the potential volunteers (Figure 1).

In 1946, Dr. Andrew C. Ivy, representative from the American Medical Association, and Dr. Leo Alexander were both sent as expert witnesses during the trials of war criminals before the Nuremberg Military Tribunals. Drs. Ivy and Alexander, with the collaboration of Brigadier General Telford Taylor, wrote the Nuremberg Code that defined a "10-point statement delimiting permissible medical experimentation on human subjects" which included as the first point: "The voluntary consent of the human subject is absolutely essential", further detailing its meaning.[24] The ethical manner in which the Yellow Fever Commission conducted its experiments with human subjects was cited in 1946, among other studies, in the Journal of the American Medical Association suggesting that it served as a point of reference in the development of the Nuremberg Code.[25]

Further developments in the field of ethics in medical research in human subjects evolved dramatically, and by 1964, the 18th World Medical Assembly, in Helsinki, Finland, adopted the "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects". These recommendations are known as the "Declaration of Helsinki". One of the basic principles of the declaration states that "In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail" also further detailing the characteristics of the informed consent.[26] The consent form used by the Yellow Fever Commission, well ahead of its time, met most of these criteria as compared to other several examples of historical "documented cases of legal informed consent" in the practice of medicine, that have been published in the literature.[27,28]

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.

Acknowledgements

The autor wishes to express appreciation to COL David N. Taylor and James Writer, MPH, for their helpful comments on this paper.

References

1. Keperlman LC, Connel DB, Gunn WJ. Effect of a monetary sanction on immunization rates of recipients of aid to families with dependent children. JAMA 2000;284:53-59.
2. Davis MM, Lantos JD. Ethical considerations in the public policy laboratory. JAMA 2000;284:85-87.
3. Marshall E. Gene therapy on trial. Science 2000;288:951-957.
4. Malakoff M. Flawed cancer study leads to shake-up at University of Oklahoma. Science 2000;289:706-707.
5. Marshall E. HHS plans to overhaul clinical research rules. Science 2000;288:1315-1316.
6. Marshall E. Harvard's Koski to lead human subjects office. Science 2000;288:1349.
7. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med 2000;342:921-929.
8. Angell M. Investigator's responsibilities for human subjects in developing countries. N Engl J Med 2000; 342:967-969.
9. Ethics of placebo-controlled trials of zidovudine to prevent the perinatal transmission of HIV in the Third World. N Engl J Med 1998;338: 1003-1005.
10. Levine RJ. The need to revise the declaration of Helsinki. N Engl J Med 1999;341:531-534.
11. Brennan TA. Proposed revisions to the Declaration of Helsinki –Will they weaken the ethical principles underlying human research? N Engl J Med 1999;341:527-531.
12. Reed W, Carrol J. The prevention of yellow fever. Public Health Papers and Reports. Presented at the Twenty-Ninth Annual Meeting of the American Public Health Association; September 16-18, 19 and 1901;20. Buffalo (NY). Columbus (OH): The Berlin Printing Company, 1902;Vol. XXVII:113-129.
13. Holbreck HB. Report of the Committee of Etiology of Yellow Fever. Public Health Papers and Reports. Presented at the Twenty-Sixth Annual Meeting of the American Public Health Association. September 1898;27-

30. Ottawa, Canada. Columbus (OH): The Berlin Printing Company, 1898; Vol. XXIV:116-127.
14. Gorgas WC. Sanitation in the Canal Zone. JAMA 1907;Jul 6:6-8.
15. Holbreck HB. Report of the Committee of Etiology of Yellow Fever. Public Health Papers and Reports. Presented at the Twenty-Seventh Annual Meeting of the American Public Health Association; October 31, and November 1899;1-3. Minneapolis, MN. Columbus (OH):The Berlin Printing Company, 1900;Vol. XXV:24-32.
16. Reed W, Carroll J, Agramonte A, Lazear JW. The etiology of yellow fever. –A preliminary note. Public Health Papers and Reports. Presented at the Twenty-Eight Annual Meeting of the American Public Health Association, October 1900;22-26. Indianapolis, IN. Columbus (OH):The Berlin Printing Company, 1901;Vol. XXVI:37-53.
17. Reed W, Carroll J, Agramonte A. The etiology of yellow fever and additional notes. JAMA 1901;Feb 16:431-439.
18. Finlay CJ. President's address. Public Health Papers and Reports, Vol. XXX. Presented at the Thirty-Second Annual Meeting of the American Public Health Association, January 1905;9-13. Havana Cuba. Columbus (OH): The Berlin Printing Company, 1905:1-7.
19. Lee B. A tribute to Carlos J. Finlay for his distinguished services to science and humanity in the discovery of the propagation of yellow fever. Public Health Papers and Reports. Presented at the Thirty-Second Annual Meeting of the American Public Health Association, Havana, Cuba January 9, 10, 11, 12, 13. 1905. Columbus (OH): The Berlin Printing Company 1905;Vol. XXX:8-14.
20. Gorgas WC. The results of yellow fever sanitation in Havana, Cuba, for the Year 1901 up to September 1st, carried on upon the basis that the *Stegomya* mosquito is the sole means of its transmission. Public Health Reports. Presented at the Twenty-Ninth Annual Meeting of the American Public Health Association; 1901;September 16-20. Buffalo NY. Columbus (OH): The Berlin Printing Company, 1902;Vol. XXVII:130-133.
21. Bean WB. The Fielding H. Harrison Lecture: Walter Reed and the ordeal of human experiments. Bull History Med 1977;51:75-92.
22. Agramonte A. The inside history of a great medical discovery. Scientific Monthly 1915;1:209-237.
23. Pan-American Medical Congress held in Havana, Cuba, February 4. Etiology of yellow fever. JAMA 1901;Feb 16:461-462.
24. The Nuremberg Code. JAMA 1996;276:1691
25. The brutalities of nazi physicians. JAMA 1946;Nov 23:714-715.
26. World Medical Association Declaration of Helsinki. JAMA 1997;277: 925-926.
27. Ajlouni KM. History of informed medical consent. Lancet 1995;346:980.
28. Ruthkov IM. Beaumont and St Martin: A blast from the past. Arch Surg 1998;133:1259.