

## **History of immunology in Cuba and its main contributions as a science**

*Historia de la inmunología en Cuba y sus principales aportes como ciencia*

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**Received:** 30/08/2023

**Accepted:** 27/11/2023

**How to cite this article:** Fuentes Rodríguez E, Vilorio Pérez C, Moreno Barreiro DC, Rodríguez Herrera E. History of immunology in Cuba and its main contributions as a science. Med. Es. [Internet]. 2024 [cited access date]; 4(1). Available in: <https://revmedest.sld.cu/index.php/medest/article/view/192>

### **ABSTRACT**

**Introduction:** the discipline of immunology emerged when it was observed that individuals recovered from certain infectious disorders were later protected against the disease.

**Objective:** describe the history of immunology in Cuba and its main contributions as a science.

**Methodological Design:** a bibliographic review was carried out through the historical-logical method using a total of 29 bibliographies obtained from the SciELO, PubMed and the Google Scholar search engine databases. Published literature that was relevant and adjusted to the topic was considered as a selection criterion.

**Development:** throughout the history of Cuba, various epidemics and diseases have emerged that have greatly affected the country's population. This has been the driving force for the development of immunology as a science in Cuba and for brilliant scientists to stand out in the fight against these diseases through their discoveries in the field of this science.

**Conclusions:** Cuban scientists dedicated to the study of immunology showed a high level of capacity and knowledge of this science, making important contributions and facing epidemics in their respective times. After the revolutionary triumph, immunology began to be developed in Cuba as a specialty, and after the founding of biotechnological scientific centers, the development of this science in Cuba was promoted.

**Keywords:** Contributions; History; Immunology

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## RESUMEN

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**Introducción:** la disciplina de la inmunología surgió cuando se observó que los individuos recuperados de ciertos trastornos infecciosos quedaban protegidos después contra la enfermedad.

**Objetivo:** describir la historia de la inmunología en Cuba y sus principales aportes como ciencia.

**Diseño Metodológico:** se realizó una revisión bibliográfica a través del método histórico-lógico utilizando un total de 29 bibliografías obtenidas de las bases de datos de SciELO, PubMed y el motor de búsqueda de Google Académico. Se consideró como criterio de selección aquella literatura publicada que poseyera relevancia y ajuste al tema.

**Desarrollo:** a lo largo de la historia de Cuba han surgido diversas epidemias y enfermedades que han afectado en gran medida a la población del país. Este ha sido el motor impulsor para que se desarrollara la inmunología como ciencia en Cuba y que brillantes científicos se destacaran en el combate de dichas enfermedades a través de sus descubrimientos en el campo de esta ciencia.

**Conclusiones:** los científicos cubanos dedicados al estudio de la inmunología mostraron un alto nivel de capacidad y conocimiento de esta ciencia, logrando importantes aportes y enfrentando las epidemias en sus respectivas épocas. Después del triunfo revolucionario se comenzó a desarrollar la inmunología en Cuba como especialidad, y luego de la fundación de centros científicos biotecnológicos, el desarrollo de esta ciencia en Cuba fue impulsado.

**Palabras clave:** Aportes; Historia; Inmunología

## INTRODUCTION

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Immunology, like all sciences, developed gradually from everyday situations. Let us remember that in its beginnings the concept of immunity was used rather to describe the privilege of some people (kingdom, government, bourgeoisie or clergy) to renounce certain social obligations. On the other hand, the biological meaning of immunity, which also means a state of exception, began to be used mainly to indicate the innate or acquired resistance of individuals to the development of infectious diseases. <sup>(1)</sup>

The discipline of immunology was born when it was discovered that individuals who recovered from certain infectious diseases were subsequently protected against the disease. It is believed that the first reference describing immunological phenomena was written by the historian of the Peloponnesian Wars, Thucydides, in 430 BC. This text describes that during a plague in Athens, only those who recovered from it could cure the sick, because they would not get sick again. <sup>(1)</sup>

Medicine in Cuba has gone through a long process of transculturation, since it originated in the aboriginal communities that inhabited the island when it was discovered and was influenced by the process of modifications associated with the Spanish conquest and colonization. To fully understand the history of Cuban medicine, it is necessary to examine its origins and organization, as well as the factors that influenced its development since it emerged as a social practice. <sup>(2)</sup>

Cuban immunology, although it did not have its own identity as a profession, was associated with the most important advances and discoveries that since the colonial period influenced the social and human development of the country and other nations. The historiographic literature on events and characters related to Cuban immunity research is extensive and varied, ranging from very specific topics such as the acquisition and application of vaccines and serums, to more general topics such as the hygienic perspective. <sup>(3)</sup>

The development of science, technology and innovation in Cuba has been a key factor for the socialist project, under the inspiring guidance of Commander in Chief Fidel Castro. As early as January 15, 1960, Fidel expressed in an event held by the Speleological Society of Cuba: "The future of our country has to necessarily be a future of men of science, it has to be a future of men of thought, because it is precisely what we are sowing the most; What we are sowing most are opportunities for intelligence (...)". <sup>(4)</sup>

The development of immunology in Cuba has had milestones that - in addition to its relevant social impact due to its usefulness in the study, control and elimination of diseases - have marked the development of medicine and other sciences in the country, and even internationally. <sup>(5)</sup>

Due to the importance of knowing about this topic, this article has the objective of describing the history of immunology in Cuba and its main contributions as a science.

## **MATERIALS AND METHODS**

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A bibliographic review was carried out in relation to the topic, using the historical-logical method. The information was searched in the databases of SciELO, PubMed and the Google Scholar search engine. The descriptors "Immunology", "History of medicine in Cuba", "History of immunology in Cuba", "Main contributions of Cuba to immunology", "Important prominent scientists in the field of immunology in Cuba" and their translations into the English language. A total of 29 articles were selected, based on their relevance and adjustment to the topic. Of them, 48 % were from the last 5 years. Ethical aspects were taken into account. The bases of the cited statements were respected.

## **DEVELOPMENT**

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### **Aboriginal stage and discovery of America by the Spanish**

We cannot speak of aboriginal knowledge about the principles and applications of immunity, since the populations inhabiting the island were not advanced cultures compared to Meso and South American civilizations. However, the medicine of the populations living in Cuba at the time of the arrival of Europeans used plants with potential immunomodulatory effects on diseases whose pathophysiology is related to immunology. <sup>(3,6)</sup>

Although the aboriginal cultures in Cuba had no knowledge of immunology as a science, they were able to use nature to their advantage to treat the diseases that afflicted them.

## Colonial Stage

As a consequence of the industrial revolution that took place in the main countries of Europe during the 18th century, trade increased between all continents and with it infectious diseases spread in an inconceivable way. <sup>(8)</sup>

Although the first experience of vaccination with an infectious agent to obtain immunity dates back to China and India in the year 200 BC, the first vaccination of our era was carried out against cowpox in the year 1718, by Lady Mary Wortley Montagu. In England in 1796, Edward Jenner practices smallpox virus inoculation during the smallpox epidemic. In this way, he managed to demonstrate his immunity against the human smallpox virus after that procedure. This is the beginning of a new era where vaccination achieved an undeniable advantage against various infectious agents that had devastated the population for centuries. <sup>(6,7)</sup>

To combat smallpox, the inoculation of pus from the lesions that caused the infection had spread in Europe. This method, not without risks and controversies, was the first to reach Cuba. On December 29, 1789, it was applied by the surgeon José Pérez Aparicio, at the request of the naval commissioner Francisco Campuzano to protect the latter's two sons, who later suffered from a benign form of the disease. <sup>(3)</sup>

Tomás Romay Chacón was the main architect of the introduction of the smallpox vaccine in the country, even before the arrival on the Cuban shores of the Royal Philanthropic Vaccine Expedition (1803-1806), commanded by Francisco Xavier Balmis and intended to propagate the condom for the Spanish dominions. The vaccine was distributed free of charge and was the first time on the Island that government authorities offered a means of protection to any member of society. It can be said that this was the first manifestation of social medicine in Cuba. <sup>(9)</sup>

Tomás Romay's achievement was of great importance because he managed to begin the vaccination of Cuba even before the arrival of the expedition from the metropolis destined to do so, which demonstrates his high level of capacity and knowledge as a doctor and scientist.

On July 13, 1804, the creation of the Central Vaccine Board of Havana was agreed. Later, Subaltern Vaccine Boards were established in other regions of the Island. <sup>(10,11)</sup>

Yellow fever provided the most powerful triumph of Cuban medicine during the colonial period. The protagonist of this victory was the distinguished Cuban doctor Carlos J. Finlay Barrés (1833-1915), who in 1881 launched an inflexible principle with mathematical precision to control the spread of diseases. When no one believed that the disease was transmitted by a simple mosquito, Finlay declared its presence as the necessary agent of transmission. Furthermore, he made very exhaustive studies on the biology of the animal and developed an original and very risky experimental technique, based on the manipulation of mosquitoes. <sup>(2,12)</sup>

Carlos J. Finlay undoubtedly deserves a privileged place in the pages of our history, since he not only stood out as a doctor, but also as a highly capable researcher. He was able to carry out a prodigious study about yellow fever and its transmitting agent.

In May 1887, the first histobacteriological and anti-rabies laboratory in our country and the Revista Crónica Médico-Quirúrgica de La Habana were founded. Both the publication and the laboratory were the work of Dr. Juan Santos Fernández. This laboratory, the first of its kind in America, marked the beginning of experimental medical research in Cuba. <sup>(13)</sup>

Another of the outstanding figures in the history of immunology in Cuba was Dr. Juan Dávalos Betancourt. He not only managed to produce the national serum according to the techniques and recommendations of its creator, Professor Roux, but also studied its adaptation to the Cuban climate. Cuba was the first country in America to distribute serum against diphtheria. That honor was shared by Dr. Domingo L. Madan in the city of Matanzas. <sup>(13)</sup>

## Neocolonial stage

Three days before the end of the first period of North American military intervention and the beginning of the Republic, on May 17, 1902, the Department of Health was created to control public health problems and institutions, as well as implement the necessary health measures. <sup>(14)</sup>

The Municipal Food Laboratory was expanded with the sections of Bacteriology, Histology and Legal Chemistry. This was the first research institution that was created in the 20th century. <sup>(15)</sup>

One of Finlay's first provisions was to change the name of the Yellow Fever Commission to the Infectious Diseases Commission, since this would study other transmissible morbid processes. The eradication of yellow fever was achieved through campaigns against the *Aedes aegypti* mosquito. It was definitively eliminated under the direction of Dr. Finlay, starting in 1908. <sup>(16)</sup>

Dr. Carlos J. Finlay also contributed to immunology in that in 1904 he presented the leukocyte criteria for a role in cellular nutrition and the formation of toxins, lysines and antibodies. <sup>(6)</sup>

In 1911, Dr. Alberto Recio Forns was sent to the United States to study the preparation of the typhoid vaccine. In 1917, Dr. Recio organized the large-scale production of the typhus vaccine in Cuba. In July 1921, BCG vaccination against tuberculosis began for the first time in Paris. <sup>(17)</sup>

Dr. Alberto Recio Forns was a brilliant scientist, since he was responsible for the introduction and preparation in Cuba of not only one, but two vaccines to combat their respective diseases.

In the field of Cuban clinical immunology, during the 20th century the description of a new type of primary immunodeficiency by Dr. Moisés Chediak Ahuayda stood out. The disease was called Chediak-Higashi Syndrome. The controversy over the authorship of the discovery has been the subject of multiple works. <sup>(5)</sup>

## **Revolutionary Triumph**

The Cuban Immunization Program was created in 1962 as a result of the political, economic and social transformations that began in 1959. The 1962 oral polio vaccination campaign was the first experience in the Region of the Americas with community and intersectoral participation. Cuba was the first country to eliminate the disease. <sup>(18)</sup>

Since the founding of the Institute of Hematology and Immunology (IHI) in 1966, the specialty of Immunology began to develop in the country. Throughout these years, numerous basic research and clinical application studies have been carried out. <sup>(19)</sup>

The Cuban biotechnology industry has its genesis in the 1980s, when a development strategy for biotechnology was proposed. As part of the outlined strategy, in 1981 the Biotechnology Front was created, of which various scientific institutions were part. From there, scientific centers began to be created throughout the country. <sup>(20)</sup>

In 1982 the Biological Research Center (CIB) was created. After the first successes of the CIB, crowned by the production of interferons, the investment process began that gave rise to the current Scientific Pole of the West of Havana. A group of more than fifty institutions, where the Center for Genetic Engineering and Biotechnology (CIGB) stands out as the leading institution; the Carlos J. Finlay Institute, dedicated to the development of vaccines; National Biopreparations Center (BIOCEN) to provide a productive channel for biotechnological achievements; the Center for Molecular Immunology (CIM), specialized in the acquisition of monoclonal antibodies; the Center for Molecular Chemistry (CQM) dedicated to the production of synthetic antigens; and the Center for Immunoassays (CIE), among other research institutes that already have regional headquarters in 12 provinces. (21)

In 2012, Cuban biotechnology companies became part of the BioCubaFarma business group. Entities from the biotechnology sector and entities from the QUIMEFA business group (in charge of drug production) joined the group, constituting one of the largest companies in the country and with the greatest economic impact, due to its income and for being an important source of employment. (20)

### **Cuba's most recent contributions to immunology**

In 1987, Cuban scientists dedicated themselves to raising the contributions of immunology, without time limits or fear, as they had to cultivate large masses of live microorganisms. An effective vaccine preparation against group B meningococcus is tested for the first time in the world. (22)

Since 1989, a recombinant streptokinase, marketed as Heberkinase, has been produced using biotechnological techniques at the Center for Genetic Engineering and Biotechnology (CIGB), which is 99,9 % pure. The studies carried out have shown that recombinant streptokinase has similar effects on hemostasis and clinical results in patients with acute myocardial infarction; Furthermore, its adverse reactions are common to those of normal SK, and it may be less immunogenic. (23)

Castellanos Fernández et al., (24) affirm in their research that one of the great achievements of Cuban biotechnology was the Heberbiovac vaccine against hepatitis B, produced by the CIGB. Starting in 1992, this vaccine became part of the national vaccination program for all newborns, and vaccination was introduced in different populations and risk groups.



In the field of clinical trials of new products, it is worth highlighting the first clinical trial in Cuba on radioimmunotherapy of high-grade gliomas with the monoclonal antibody Re-tagged h-R3 was the introduction of immunoscintigraphy in the selection of patients treated with mTc-labeled monoclonal antibodies, nimotuzumab and h14F7 immunotherapy. <sup>(25)</sup>

The Vax-COLER vaccine candidate, based on *Vibrio cholerae* O1 El Tor Ogawa attenuated strain 638, is in clinical development. Although two other vaccine candidates are made from an inactivated C7258 strain of *V. cholerae* O1 El Tor Ogawa, they are in various stages of their technological and pharmaceutical development. <sup>(26)</sup>

Ramírez Bartutis <sup>(27)</sup> has carried out studies to obtain a vaccine against dengue. This study constitutes the first scientific work worldwide that evaluates the immune response of the non-structural protein 3 (NS3) of the dengue virus 2 (DENV 2) obtained by recombinant means in *Escherichia coli*, for which the authors of this work consider this study of great relevance. It is demonstrated for the first time that this recombinant protein preserves the native antigenic determinants, is highly immunogenic and stimulates a Th1 type cellular response (T helper cells). <sup>(27)</sup>

An achievement of Cuban medicine is the recombinant human CIMAvax-EGF® vaccine, which is a therapeutic vaccine against cancer, developed in Cuba and licensed in the country for use in adult patients with non-small cell lung neoplasia in the stages IIIB and IV. <sup>(28)</sup>

Another contribution of great importance is the creation of Cuban vaccines to combat COVID-19, such as Abdala 50µg, Soberana 02, and Soberana PLUS ST. These were approved by the Center for State Control of Medicines, Equipment and Medical Devices (CECMED) for emergency use in the population. Following the approval of booster doses, the vaccine candidates Soberana 01 and Mambisa (the latter is for nasal administration) were accepted. <sup>(29)</sup>

After the revolutionary triumph, immunology had a marked boost in Cuba as a result of the transformations carried out by the Revolution, which provided important contributions to immunology as a science of great relevance at a national and international level.

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## **CONCLUSIONS**

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Confronting epidemics has driven the development of immunology since the colonial period in Cuba. The introduction, development and evaluation of

vaccines has proven to be the most effective response against them throughout history. Cuban scientists showed a high level in this field, making important contributions and facing epidemics in their respective times. After the revolutionary triumph, immunology began to be developed in Cuba as a specialty, and after the founding of biotechnological scientific centers, the development of this science in Cuba was promoted.

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## **STATEMENT OF AUTHORSHIP**

**EFR:** conceptualization, research, methodology, project administration, validation, writing the original draft, review, editing.

**CVP:** conceptualization, investigation, methodology, validation, writing of the original draft, review, editing.

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## **CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest.

## **SOURCES OF FUNDING**

The authors declare that they did not receive funding for the development of this research.