

## **ATTENTION TO THE SNAKEBITE ENVENOMING PROBLEM IN COSTA RICA: A NATIONAL PROJECT WITH GLOBAL PROJECTION**

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### **Introduction**

Snakebite envenoming is an important public health problem worldwide. This disease affects mainly people in social vulnerable conditions in rural areas in Africa, Asia, Latin America, and some countries in Oceania. It is estimated that approximately two and a half million snakebites occur every year, with almost 125,000 deaths; and, out of all the survivors, between 300,000 and 400,000 will suffer from some kind of physical or psychological sequelae<sup>1</sup>. However, it is very likely that these figures are higher, since it often happens that not all those who suffer snakebites seek medical attention at health centers, so the events are not included in the official statistics.

This is a typical “disease of poverty”<sup>2</sup>, and it is considered one of the “neglected tropical diseases” that affect almost exclusively rural populations in vulnerable conditions<sup>3</sup>. These diseases have a special impact on certain groups of people, such as indigenous populations and farmers. Since these affected sectors do not have a political voice within the decision-making entities, these diseases have received little attention from health authorities, health-promoting organizations, research agencies, and the large pharmaceutical industry. Snakebites are responsible for the death of many people, but this disease already has an effective treatment: the administration of antivenoms. The World Health Organization (WHO) has included antivenoms in its “List of essential medicines”; however, access to it is limited or inexistent in several regions of the world<sup>4</sup>.

In contrast with the situation of many countries, Costa Rica has developed a comprehensive and effective approach to deal with this problem. The country has an antivenom-production laboratory, the Clodomiro Picado Institute (ICP for its acronym in Spanish), adscribed to the School of Microbiology of the University of Costa Rica (UCR, for its acronym in Spanish), which carries out an intense activity to generate scientific - technological knowledge through research. It also coordinates an extension program that aims to share knowledge on the prevention and the proper clinical management of these envenomings. At the same time, the Costa Rican Social Security (CCSS, for its acronym in Spanish) treats snakebite envenoming cases in its hospitals, clinics, and in some EBAIS (basic centers of comprehensive health-care that constitute the primary attention level); and the Ministry of Health, as a governing entity, manages and coordinates activities related to this topic. Furthermore, health-care professionals are trained to diagnose and treat this pathology during their university studies and in their continuous training activities in their work centers.

The information about snake bites that has been shared through different communication strategies, with the participation of several institutions, has helped the population in the country learn about the basic prevention measures for these accidents, as well as what to do when they happen. This means that, after several decades of sustained inter-institutional and inter-social efforts, the country has implemented an effective comprehensive approach to manage this public health issue. In the last few

decades the success of these endeavors has gone beyond the borders of the country, and today Costa Rica is a global leader in the fight against snakebite envenoming. How did we get to this point? How was this project developed? Which factors have made possible this comprehensive, sustainable, and international development?, and what lessons could we learn from this experience to manage other topics of interest in the country and the region? This essay reviews the main milestones and stages this project has gone through and offers some general reflections about it.

### **How did the story begin?**

The first steps to tackle the problem of snakebite envenoming in Costa Rica go back to the early 20th century, particularly with the work of Clodomiro Picado Twight; but Picado admitted that people before him, like Anastasio Alfaro, had already shown interest in studying snakes in the country<sup>5</sup>. Between the years 1908 and 1913, Picado was granted a scholarship by the government, supported by the *Junta de Caridad de San José*, and did his higher studies in France, in *La Sorbonne* and the *Institute Pasteur*. Upon his return to the country, he took on the direction of the Clinical Laboratory of the San Juan de Dios Hospital (HSJD, for its acronym in Spanish), which had been established some years before. Picado was hence located in the most important medical center in the country, which had undergone significant changes thanks to the efforts of people like Carlos Durán Cartín, and the growing commitment of the Costa Rican state to the promotion of public health<sup>6</sup>. From his position in this health center Picado did an impressive work, not only implementing laboratory diagnosis as an essential arm of hospital work, but also transforming this laboratory into a high-level biomedical research center. Picado's scientific work involved many areas like Biology, Phytopathology, Microbiology, Clinical Analysis, Hematology, Pathophysiology, Immunology and others related to Experimental Medicine, which is evidenced in the more than 100 publications he did through several decades of uninterrupted work<sup>7</sup>.

One of the topics of interest for Picado and his collaborators was snakebite envenoming. Many people from rural areas who suffered these envenomings went to the HSJD. Back then not much could be done for them, since only symptomatic treatments were available, and in severe cases these did not prevent death. Picado decided to approach this topic, and did so by developing a strategy that could be defined as comprehensive. This means he not only looked for an immediate solution to the lack of effective therapies, but he also studied the topic from different angles, and promoted interventions in the public health scope to achieve a better prevention and management. His work in this topic is captured in the book *Serpientes venenosas de Costa Rica: sus venenos, seroterapia antiofídica* (Venomous Snakes in Costa Rica: Their Venoms, Antiophidic Serum Therapy), published in 1931<sup>8</sup>.

Aside from generating original scientific knowledge about snake biology, the effects of venoms at the experimental level, and the inhibitory action of natural and synthetic substances on venoms, Picado searched for solutions to the problem. Since he closely followed scientific developments around the world, it came to his attention that snake venoms in Brazil were similar to those in Costa Rica, and he learned that, since 1901, that country produced antiophidic sera at the Butantan Institute, in São Paulo<sup>9</sup>. Picado established contact with Brazilian scientists, particularly with the founder of the Butantan

Institute, Dr. Vital Brazil Mineiro da Campanha, and in later years with Dr. Afranio do Amaral, who was also the director of said institute.

Through this cooperation Picado sent venom he collected in his laboratory from the Costa Rican *terciopelo* snake (*Bothrops asper*) to Brazil. In Brazil they sent him back ampoules of antivenom serum they produced at the Butantan Institute. With these ampoules Picado created a serum bank at the HSJD, and treated people admitted to the hospital due to snake bites. In his 1931 book, Picado mentions that in the ten years after the antivenoms were introduced to the HSJD no person had died from snake bites. In our extension activities in rural areas in Costa Rica we have met elderly people who referred to the antivenom as the “Butantan Serum”, echoing those times when this product from Brazil was saving lives in our country.

At the same time, Picado was working on this topic from the scope of public policies. Since he had many connections to academic, health, and political sectors in the country<sup>10</sup>, with the help of the Minister of Public Health, Solón Núñez Frutos, Picado promoted a pioneering law in the continent called “Law of Protection against Ophidism”. Approved by the Congress and signed by the minister and the president Ricardo Jiménez Oreamuno, the law established, among other things, the prohibition of talisman sales to treat bites; the obligations of farm owners and hospitals to have antiophidic serum and the equipment for its administration, and the obligation of train drivers to transport people bitten by snakes and a companion; moreover, in the case of death of a farmer from snake bite in a farm where the owner had no antivenom deposit, the law established the obligation of the owner to pay the family of the victim, for a year, the salary the person made<sup>11</sup>.

The comprehensive approach developed by Picado to solve the problem of snakebite envenoming involved scientific and technological research, the introduction of antiophidic sera into the country, sharing information about the topic in different social sectors, and working to develop public policies for their control, and all this laid the groundwork for the national strategy on the subject. The strategy also sidestepped the reductionist trends that wanted to approach the situation from just one angle, like only producing antiophidic sera, something that has happened in other Latin American countries and other latitudes.

### **From Clodomiro Picado Twight to the Antiophidic Serum Program in the Decade of 1960**

After Picado's death in 1944, work at the Clinical Laboratory at HSJD continued under people who had grown with it, like Luis Bolaños, Hernán Badilla, and Alfonso Trejos Willis. Where snakebite envenoming is concerned, the hospital kept the serpentarium, and there was still access to the Brazilian antiophidic sera, but research on the topic decreased. During the following decades antivenoms were imported from Mexico, Germany, and the United States of America to treat envenomings in Costa Rica; however, the specificity of these sera and their efficacy were highly questioned.

The academic interest on the topic of envenomings was resumed in the early 1960's by a young professor of the Department of Biochemistry in the School of Medicine at the UCR, Jesús María Jiménez

Porras, who did his doctorate studies in Louisiana State University, USA. Jiménez studied venoms from different species of Costa Rican snakes from a biochemical point of view, and he wrote several notable publications on the topic. Furthermore, toward the end of the decade, he published an excellent bibliographic review on snake venoms<sup>12</sup>. The government of Francisco J. Orlich (1962 - 1966) considered the need for the country to produce its own antiophidic sera (antivenom), for which it requested technical support from the Embassy of the United States of America in Costa Rica. As part of this agreement, in 1965 Herschel Flowers arrived at the country. He was an American military veterinarian who had studied venoms and antivenoms, and who would play an essential role in this process in Costa Rica. Alvaro Aguilar Peralta, the Minister of Public Health during the government of José Joaquín Trejos Fernández (1966 - 1970) committed to the project and established a partnership between the Ministry, the USA Military Mission in the country through Flowers, and the UCR, initially through Jiménez Porras. Disagreements between Jiménez and Flowers led the former to walk away from the project, and in 1966 Róger Bolaños Herrera joined the team; he was the coordinator of Immunology at the School of Microbiology of the UCR<sup>13</sup>.

Thus, the Antiophidic Serum Program was born, attached to the Ministry of Public Health, and Róger Bolaños coordinated every technical and scientific aspect. Thanks to this program and to the commitment and dedication of its members, in March 1967 the first batch of “polyvalent antiophidic serum” was produced in Costa Rica, the antivenom capable of treating snakebite envenomings by most of the Central American snakes, with the exception of the coral snakes and the sea snake. That same year, the first batch of an “anti-coral antiophidic serum” was produced, which was effective against coral snakebites. It should be highlighted that, even if the original purpose of this program was to produce antiophidic sera in the country, the overall philosophy established by Picado Twilight was maintained, and in 1967, through a presidential decree, the National Commission Against Ophidism was created, which had an array of functions, like the research and study of snakes and envenomings, technical counseling for official organizations about the topic, establishing relationships with related foreign institutions, organizing activities to share knowledge on snakebite envenoming, and elaborating law projects or regulations about the subject<sup>14</sup>. This comprehensive approach shaped the strategy implemented in the country to face this problem. Likewise, the joint efforts of the Ministry of Public Health, the CCSS, and the UCR strengthened and favored synergies that helped ensure the success of these first steps, and laid the foundations for a long lasting national project.

### **The Origins of the Clodomiro Picado Institute**

The success of the Antiophidic Serum Program motivated the Ministry of Public Health to create an institute which would be responsible for producing the antivenoms and for managing the efforts carried out in the country on this subject. Thus, the Clodomiro Picado Institute (ICP) was created in 1970 as an agency of the ministry. Due to the natural leadership skills of Róger Bolaños, who was still working as a full time professor at the UCR, he was appointed director of the institute. Aside from his known scientific capacity, Bolaños demonstrated great competence as a manager and great commitment to the project. Since the early days of the institute, he promoted the previously mentioned integrated philosophy.

Bolaños had the clarity to understand that the project would be better managed by the UCR, so negotiations began between the university and the ministry, which concluded by signing an agreement in 1972 stating that the ICP was an agency of the UCR. This decision was important because it ensured the control of the project by a higher education institution governed by a philosophy of academic excellence, equity, and common good. These aspects were essential for the project because its main mission was to solve a health problem that affected vulnerable sectors in rural areas. Also, being a part of the UCR helped the institute avoid any political upheavals that could have affected the continuity of the program.

Since its early days, Bolaños and his colleagues at ICP established a holistic development that included four main areas: production and quality control of antivenoms; scientific and technological research to learn about snakes, their venoms and envenomings, to innovate the technology of antivenom production and generate new products; social extension to encourage prevention and adequate management of envenomings; and undergraduate and graduate university courses to contribute to the training of professionals and academics in the country and the region. These four arms simultaneously strengthen each other and they are strongly linked together. This model has been maintained and consolidated over nearly 50 years, and constitutes a bastion over which this project has developed.

Bolaños and his colleagues at ICP also managed to create a group culture based on teamwork and cooperation, and on the belief that the contributions of each person are essential to achieve common goals. They managed to instill respect for the collective agenda and the conviction that individual agendas should be related to the collective goals, in the framework of a common purpose. This appreciation of each person's work is a central element of ICP culture. The introduction of a work ethic and a commitment to comply with institutional goals was also essential. These elements have been embedded in ICP mission, which is to help solve the problem of envenomings caused by bites and stings by venomous animals in Costa Rica and other countries; the institute also aims to help national scientific and technological development through a group effort that involves research, teaching, social action and production activities. It is important to highlight that throughout almost five decades the different directors of the ICP (Róoger Bolaños, Luis G. Cerdas, José María Gutiérrez, Gustavo Rojas, Yamileth Angulo and Alberto Alape) have respected and encouraged this central philosophy, focusing on different aspects depending on the circumstances of the moment, and this has allowed the continuity and strategic direction of the project. The main development aspects of the central line of action of the ICP are described next.

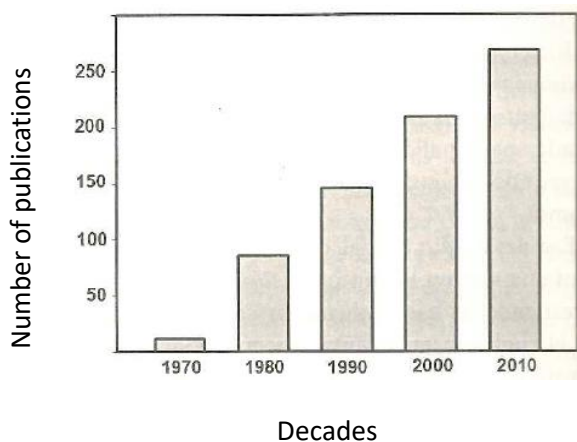
### **Generation of knowledge through research**

Since its creation, the ICP developed a sound research program on the topics of snakes, venoms, envenomings, and antivenoms; Bolaños clearly encouraged this aspect of the institutional work. This should be considered under the context of what the ICP represented since its origins: a small group of people, most of whom did work related to the production of antivenoms. Under these circumstances there was a risk that the little resources available would be used only for the main function: producing

the needed antivenoms. This had happened in several antivenom production laboratories in Latin America, where the production took up all the energy and there was no room left for research. Bolaños had the vision to sidestep this risk, and even with the existing limitations he promoted research. The ICP has published abundant research works since its creation<sup>15</sup>, and graduate and postgraduate students and researchers have joined the project gradually. Bolaños not only promoted research, but since the beginning he encouraged a balance between basic and applied or technological research; in other words, he clearly understood that scientific development had to be comprehensive.

Even with all the administrative duties he had as director of ICP, Bolaños also found time to teach students how to carry out research. He would assign a different project to each student, and encouraged them to review scientific journals he brought himself from the UCR library. He taught them how to write scientific articles through a praiseworthy work. This is how the research group at ICP started to take form, and it matured with the passing of time. There were international connections since the beginning, and in 1976 Bolaños organized a world congress in Costa Rica for the International Society on Toxinology, to which over 250 people attended. This activity created links between the ICP and the most important personalities in Toxinology around the world, which catalyzed the endogenous academic processes.

This continuous initial development became an upward spiral based on a select group of researchers with doctoral degrees, which has grown and consolidated through the decades, and today it constitutes a group of excellent academic level and high scientific productivity. A broad research agenda has been developed in topics related to the biology of venomous snakes, the biochemistry and toxicology of venoms and their toxins, the analysis of the mechanism of action of venoms in the organism, the search for venom toxin inhibitors, the epidemiology of snakebites, the study of the pre-clinical efficacy of antivenoms, and the continuous improvement of antivenom production technologies, as well as new topics related to bacterial toxins and venoms from other groups of animals<sup>16</sup>. The development and impact of the research done at ICP are evidenced in the quantitative and qualitative growth of the scientific publications and on the high number of citations of ICP works on the international scientific literature<sup>17</sup>. The following chart shows the number of publications that include authors from ICP in the nearly five decades of existence of the institute, up until the year 2017.



Since its origins, but especially during the decade of 1990, ICP established strong international links in research, participating in academic networks with groups from every continent<sup>18</sup>. This international scenario has brought on many positive consequences, like granting access to technologies and laboratory methods lacking in the country, offering aid to approach ambitious scientific investigations, encouraging the exchange of researchers and students between Costa Rica and other countries, consolidating the academic training of the research personnel at the ICP, facilitating experiences abroad for Costa Rican students, and contributing with groups from other countries, especially in Latin America, in the training of their own academic frameworks, and making visible the national scientific activity in varied academic contexts, which has catalyzed new collaborations in a process of connections and alliances. The academic dynamics at the ICP has also helped consolidate the research community in Costa Rica, since undergraduate and graduate students have done their thesis projects at the ICP, and then continued their academic and professional careers in other national or foreign institutions. Researchers at ICP have also taught courses in undergraduate and graduate programs in other academic units of the UCR, especially in the School of Microbiology, to which ICP is adscribed. The following image shows the countries where ICP has established academic collaborations with research groups; every red dot corresponds to a country where cooperation with one or more groups has been developed.



The construction of this body of knowledge on snakes, venoms, antivenoms, and snakebite envenomings has not only contributed to the scientific domain, but it has also offered inputs to improve the way in which envenomings are managed. On one side, it has helped to better understand their pathophysiology and the identity of the venom toxins that determine snakebite-induced pathology. This information has been shared with the health care professionals in the country and abroad through continuous education activities. Epidemiological studies have provided information to identify the regions in the country where envenomings occur more often, so antivenom distribution can be programmed accordingly; these data are useful for decision makers when determining how to distribute the antivenoms. Furthermore, knowledge has been generated to support snake and reptile conservation programs. The in-depth study of venoms and of the immune reactivity of antivenoms has generated evidence to learn which products are effective against which venoms, both in Costa Rica and other latitudes. ICP has developed a methodological platform to evaluate the neutralizing ability of antivenoms against the toxic effects of venoms. This methodology has been used to characterize

antivenoms from different regions in the world, which has offered data that reveal which antivenoms are effective in a specific region<sup>19</sup>.

The idea that research must be developed comprehensively has prevailed at ICP, and it coincides with the way in which research has evolved at the UCR in general. The university has encouraged the development of knowledge in every academic area and from very different perspectives. This philosophy diverges from the leading positions of national authorities in science and technology in Costa Rica, and from other sectors which have a vision of research that focuses in areas and topics that have a direct economic impact, distorting what should be a comprehensive scientific development. ICP has maintained a balance between basic scientific research and applied or technological research.

### **Sharing Knowledge on Snakebites with the Population**

The country has done an important effort to share, through different means and strategies, basic information about snakes and envenomings, encouraging the population to learn about this subject. Since its beginnings, ICP has implemented a social action program that has consolidated through time. The development of these activities in the early 1970's came hand in hand with the establishment of social action as one of the three central missions of the UCR, after the III University Congress (1971 - 1972). This program has helped share knowledge about the topic in different sectors, like communities in regions of high incidence of envenomings, rural and urban labor groups, public institutions, companies, and student sectors, among others. Researchers and students have participated in this program through the University Community Service project (TCU, for its acronym in Spanish, at the UCR). A notable project was carried out in the Cabecar indigenous communities at Alto Chirripó, in which a prevention and management manual was edited in the Cabecar language<sup>20</sup>, and it was shared with the Bribri and Ngabe indigenous communities in their own languages. The media, especially the communication department at UCR, collaborated with these efforts by sharing news and comments regularly that included instructions on how to prevent and handle an accident of this nature. Community involvement has been important in this action framework because organized sectors frequently ask for the services of the ICP and offer information inputs and visions that help enrich the work done at the UCR.

An important contribution of the ICP has been the continuous education program for the health care personnel, mainly physicians and nurses, regarding the diagnosis and treatment of envenomings. This activity has been going on for several years in hospitals and clinics of the CCSS, as well as in university schools of the health care area. Medical and nursing symposia have also been done on the subject. The continuous teaching activities of the CCSS have allowed health care professionals to have an updated knowledge on the diagnosis and clinical management of these cases. This is a key aspect of all the actions needed to control this problem. These continuous education activities have extended to other countries in the Central American region, as well as in Colombia and Ecuador.

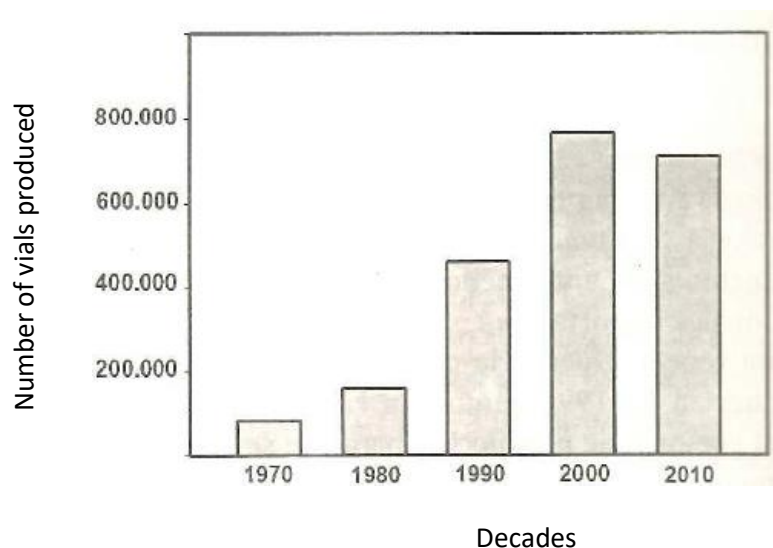


### Technological Development and Antivenom Production: From Local to Global

At first, ICP produced the antivenoms the country needed during the decade of 1970, which represented an average of 8,000 vials per year, that were distributed to the CCSS, and to the Ministry of Public Health. The experience accumulated by the group of professionals and technical personnel in charge of the production, and the constant innovations they implemented, helped gradually increase the production volume of antivenoms. The incorporation of ICP to the UCR catalyzed the innovation and encouraged the development of thesis projects focused on improving the production, at first in the School of Chemical Engineering of the UCR, and then in other academic units, among which the School of Microbiology offered an important participation from its students, who were working on their Final Licentiate Degree Graduation Projects, which complemented the research developed by the group of ICP.

A quality leap happened in the early 1990's, when the institute adapted to a new methodology to produce antivenoms<sup>21</sup>. This technology is used today in several antivenom producing laboratories around the world. Three additional and important factors that influenced the development of antivenom production were the construction of a production facility in 1991, the decision to specialize the production personnel so they could exclusively dedicate to this activity, and the creation of the Technological Development Section (SEDETEC, for its acronym in Spanish), which brought together a group of researchers who focus on improving antivenom production technologies and on developing new products. This accelerated the innovation processes for antivenom production. As a consequence, SEDETEC developed a new methodology of human plasma fractionation, with the objective of purifying immunoglobulins and albumin<sup>22</sup>. This novel technology, patented by the UCR, can also be applied for antivenom production and it is intended to be used in the ICP antivenom facility in the future<sup>23</sup>.

Thanks to this, ICP managed to improve its production, both qualitatively and quantitatively. The average yearly average of antivenom produced rose from 8,000 vials in the decade of 1970, to 110,000 vials in 2016. The following graph shows the number of antivenom vials produced at ICP in each one of its five decades of existence, up until 2016.



It is important to highlight that ICP and the UCR in general have defended the advantage of producing antivenoms, a strategic product for public health that has a limited profitability margin, in the public sector. Examples of private producers which have suspended their antivenom production line due to profitability reasons confirm the position of the UCR<sup>24</sup>. This option, however, demands public investment policies to maintain and make this production grow, and to comply with international regulations on the matter, something that becomes difficult with the fiscal situation of the country. On the other hand, some university sectors have expressed their concerns about this increment in production, stating that the growth of the production sphere of ICP could decrease their academic development. Evidence suggests that this has not happened; on the contrary, a strong simultaneous development has been observed in these two lines of action, as well as in the extension and teaching activities.

The increase of antivenom production gave way to the possibility of distributing these products to other countries, to collaborate with the solution to this problem beyond our borders. Aside from the fact that this has helped improve public health, the increased production and distribution of antivenoms has generated an important income that has allowed, on the one side, the operations of the institute, especially for the production of antivenoms, and on the other side, to invest in infrastructure, equipment, and hiring new personnel, all of which contribute to a sustained growth dynamics. With the evolution of the ICP, the academic, social and economic activities have also evolved. The expansion beyond Costa Rica began in every Central American country and, recently, it has covered the demand of antivenom in Ecuador, with possibilities of distribution also to Colombia, Perú and the Caribbean island of Santa Lucia. With the new millennium, several south-south cooperation projects began that have allowed the development of new antivenoms for some countries in Sub-Saharan Africa, Papua New Guinea, and Sri Lanka. It is interesting to notice that some documents from the early days of ICP reveal that Roger Bolaños always had a vision that the ICP had to collaborate with the solution of this problem in other countries, and he was already thinking of expanding the production to cover the Central American region. Bolaños proposed this sort of initiatives to the Panamerican Health Organization (PAHO), and to the Central American University Council (CSUCA). This ambitious dream came true several decades later.

### **The Importance of being at the UCR**

The previously described processes, which reveal a comprehensive and holistic approach in the face of a public health problem, originated and consolidated in a favorable institutional context which was compatible with the foundations that guided these efforts. A project of this nature would probably never have consolidated in an environment characterized by the values and visions that have prevailed in the ideological arena of Costa Rica in the past few decades, especially since the decade of 1980. This political context is characterized by neoliberal trends that put a priority in economic profitability and deregulations, reducing the role of the public sector in the national life, hence weakening the values of solidarity and search for equity. The UCR, while facing difficult and contradictory situations, has been able to maintain the foundations of high standards and search for the common good that are embedded

in the Organic Statute of this institution. The project developed in ICP fits perfectly with these foundations, so the described processes have been supported and nurtured by the authorities of the UCR and the university community in general. This is an element that must be taken into account when understanding the processes discussed in this essay.

### **The Role of Public Health Development in Costa Rica**

To understand the success the country has had in the topic of snakebite envenoming, it is important to analyze the notable national developments in the area of public health<sup>25</sup>. In this context, the efforts of ICP have focused on a national institutional framework that has facilitated its projection. On one side, the wide coverage of health services, which extends to the whole national territory, has allowed people who suffer from snakebite accidents to have access, in a short period of time, to a health center. On the other side, the CCSS has an antivenom acquisition policy that guarantees the provision of this essential medicinal product to every health center that needs it, including hospitals, clinics, and EBAIS in areas of high snakebite incidence.

There has also been a permanent coordination between the Ministry of Health, the CCSS, and ICP, so that they have worked together to elaborate treatment protocols and share discussions on the topic. This has been complemented by permanent continuous education programs to train the health care professionals of the CCSS on basic aspects of envenoming management. International analyses on the successful approach to this health problem have underscored the relevance of these aspects, meaning the wide acquisition and distribution of antivenoms by health care institutions, training the medical and nursing staff, and above all, strengthening the health care system in general<sup>26</sup>. In the current paradigms of global health, the management of specific diseases is not conceived from a “reductionist” perspective, but it is considered within the development of the public health care system as a whole, with “diagonal” approaches through which the management of a specific problem strengthens the health care system in general, and vice versa<sup>27</sup>. A solid health care system which has a wide coverage allows the prevention and attention of multiple diseases, and favors synergies of many kinds. This is precisely what happened in Costa Rica with the topic of snakebite envenomings.

### **Going Beyond Borders: Regional Cooperation Networks in Latin America**

With the new millennium, the action framework of ICP and Costa Rica regarding snakebite envenoming highly increased in its international projection. In Latin America ICP has led regional initiatives to create cooperation networks. Since its origins, ICP offered technical advice to institutions in Colombia, Ecuador, and Peru on the topic of antivenom production and quality control, and has served as a reference center for the PAHO on this subject. In the decade of 1990 ICP was declared a reference center on the topic of snakebites in the Central American region by the Council of Ministers of Health of Central America (COMISCA). Furthermore joint research projects and academic exchanges have been established with groups in Mexico, Guatemala, Honduras, Nicaragua, Panama, Colombia, Venezuela, Ecuador, Peru,

Bolivia, Brazil, and Argentina. These processes were consolidated in 2006 through a regional project supported at first by the Ibero-American organization CYTED (Science and Technology for Development), and then by the FEMCIDI program of the Organization of American States (OAS). In addition to many groups in Latin America, these regional programs have had the participation of the Biomedicine Institute of Valencia in Spain, which is a part of the Spanish National Research Council (CSIC, for its acronym in Spanish) of that same country.

These projects coordinated by ICP included the participation of public institutions in eleven countries. This initiative led to the organization of regional workshops on the topics of antivenom production, quality control, and distribution<sup>28</sup>. Technical and professional personnel were trained through internships and a collaborative research was developed to study the neutralizing ability of the antivenoms produced in the country, which has been the largest pre-clinical antivenom study project in the region<sup>29</sup>. A cooperation network was left in place after these initiatives concluded, and it has strengthened the production and control of antivenoms in Latin America with the objective of turning this region into a self-sufficient area in terms of provision of the antivenoms needed in our countries. Today, ICP participates in an initiative led by the PAHO to implement a regional plan in Latin America and the Caribbean on the topic of envenomings from poisonous animals.

### **Beyond the Continent: New South-South Cooperation Processes**

In February 2001, ICP participated in a WHO meeting where the global situation of antivenom production and quality control was analyzed<sup>30</sup>. During this meeting the representatives from Nigeria mentioned the alarming shortage of antivenoms in sub-Saharan Africa. So, several participants, among those ICP, offered a possible solution to the problem: laboratories in other regions of the world would offer part of their capacity to produce antivenoms for Africa. ICP joined an international partnership that included the Health Ministry of Nigeria, and colleagues from Oxford University and the Liverpool School of Tropical Medicine, both in the United Kingdom, to produce antivenoms for Nigeria. Nigerian snake venoms were sent to Costa Rica and the antivenom was produced; at first it was called Pan-African antivenom, and then it was designated EchiTab-plus-ICP<sup>31</sup>. It must be highlighted that this project represented a special effort from ICP, because at the time it was having trouble producing the required volume of antivenoms for Latin America; however, there was a sense of solidarity in the authorities and staff at ICP, and they took on the commitment to collaborate with African countries on this topic.

Several batches of the antivenoms for Nigeria were produced, and their neutralizing capacity was assessed at the pre-clinical level, using experimental laboratory tests, with positive results. Afterwards the antivenom was donated to be assessed in a clinical trial in the community of Kaltungo, in Nigeria. The results of the study were highly satisfactory in terms of the efficacy and safety of the antivenom<sup>32</sup> and the product was registered in the Ministry of Health of Nigeria, and in 2011 its regular export process began. Afterwards, this antivenom was registered in Burkina Faso and Mali, and more recently it was distributed in Benin. Then, when the antivenom produced by the company Sanofi-Pasteur was withdrawn from the African market, the organization Médecins sans Frontières (MSF) decided to use the

ICP antivenom to treat envenomings in their hospital center in the Central African Republic. More recently, ICP has developed a new antivenom with a wider coverage, and it could eventually be used in other African countries beyond the western region of the continent<sup>33</sup>.

After this project began in Africa, another collaborative effort started with colleagues from the universities in Papua New Guinea and Melbourne, Australia, with the purpose of producing a new antivenom to treat envenomings by the taipan snake (*Oxyuranus scutellatus*), which has one of the most toxic venoms in the planet. The reason for this study was that, even though the antivenom producer in Australia offers effective antivenom against the taipan snake, its cost is too high for Papua New Guinea, so there is a shortage crisis in this country. Thus a new anti-taipan venom was produced at ICP<sup>34</sup>, and it proved to be effective on a pre-clinical level; then it was analyzed in a clinical essay in Port Moresby, Papua New Guinea. The antivenom proved to be effective and safe, and ICP plans to produce it regularly in the future for its distribution.

These South-South intercontinental projects motivated a non-governmental organization in California, Animal Venom Research International (AVRI) and colleagues from the University of Peradeniya in Sri Lanka to ask ICP to develop a specific antivenom for Sri Lanka. This country has over 30,000 cases of snakebites per year, and it depends on antivenoms from India for its treatment, but these antivenoms have revealed to have limitations in their safety and efficacy profiles. The new project began, this time focusing on transferring technology from Costa Rica to Sri Lanka, so the country can develop its own antivenom producing facility. This constitutes a new step in the projection processes of ICP, because this first technology transference experience could later be projected on to other countries that need to establish their own antivenom production laboratories. As an initial step, a pilot batch of polyvalent antivenom was produced for Sri Lanka; it was assessed on a pre-clinical level and today it is being studied in a clinical trial in that country<sup>35</sup>.

### **Beyond Production and Research: The Projection of a Model to Face Snakebite Envenoming on a Global Scale**

The experience accumulated in Costa Rica to face this health problem, based on a holistic approach that contemplates knowledge development through antivenom development, production, and distribution, cooperation and training, health care professional training, prevention campaigns in communities, and establishing international cooperation networks has helped Costa Rica to project this vision on an international scale. An initiative of ICP and the Ministry of Health, together with the Ministry of Foreign Relations, through the Costa Rican Permanent Mission to the United Nations in Geneva, with the participation of 18 countries from every continent, and with the support of the organizations Global Snakebite Initiative (GSI), Health Action International (HAI) and Médecins sans Frontières (MSF), proposed an event on snakebite envenoming in the World Health Assembly celebrated in Geneva in May, 2016. The purpose of the activity was to draw the attention of the WHO and the state members to the severity of the snakebite envenoming problem.

After this event, a group of countries and other stakeholders have come together to drive forward international initiatives on the topic, with Costa Rica playing a leadership role. This has put the topic of snakebite envenoming on the maps of the WHO and PAHO, and other international organizations, including the Kofi Annan Foundation; these developments have greatly changed the global scenario of attention of this topic. In 2017, Costa Rica and a group of 21 countries submitted a technical dossier to the Strategic and Technical Advisory Group (STAG) of the WHO for neglected tropical diseases, in which they requested the inclusion of snakebites in the official list of the WHO for these diseases<sup>36</sup>. The request was approved and snakebite envenomings have been cataloged as a Category A disease in the WHO list of neglected tropical diseases. This step added an important political topic on a global scale, and has generated a series of initiatives driven by different actors to give more attention to the topic. After this decision, the Department of Neglected Tropical Diseases of the WHO began drafting a global plan to control this disease.

Afterwards, in January 2018, the Executive Committee of the WHO accepted a resolution proposal presented by Costa Rica and Colombia, and supported by a group of 18 countries, for this organization to urge the state members to adopt a series of programs and policies to improve prevention, management, and treatment of envenomings, a resolution that was approved by the World Health Assembly on May 2018<sup>37</sup>. The approval of this resolution in the most important global public health organization represents a milestone in the efforts to develop effective interventions to reduce the impact of these envenomings. All these accomplishments, in which Costa Rica's participation has been essential, foretell changes in the attention this topic will receive globally. The described international progress has been possible thanks to a never-before seen collective process in which Costa Rica's efforts have been vital, in a well-coordinated context that has had the participation of many other countries, the WHO, and its regional offices, organizations that promote the attention to this topic, media sectors, and the academic community. This is a clear example of how joint initiatives by different stakeholders around a public health topic, with a clear collective agenda, can yield positive results.

## **Conclusions**

The collective and long lasting efforts that Costa Rica has developed to understand and find solutions to the problem of snakebite envenomings invite to reflect on topics of political, scientific, and technological nature that transcend the issue of snakebites and help us analyze other topics and work areas. On one side, it is clear that the success in the management of a complex problem requires the integration of multiple sectors under a frame of cooperation for a prolonged period of time. In Costa Rica, ICP has taken on the leadership to deal with this topic in collaboration with the health care system institutions, and more recently, with the Ministry of Foreign Relations, through the Costa Rican Permanent Mission to the United Nations in Geneva. Furthermore, synergies have been established with national and international communities and institutions, and international cooperation networks have been developed with research groups, ministries of health, non-governmental organizations, and foundations. These different actors have allowed the successful approach to these complex and difficult tasks.

The consolidation of a program like the one created at ICP had a strong impact on the country because, for several decades, Costa Rica has promoted an important development in the health sector, providing services all around the country, and training qualified personnel; it has also guaranteed the access to antivenoms to the whole population, without a direct cost on the patients. The history of this national effort also evidences that the approach to complex problems demands a comprehensive strategy that combines the generation of knowledge with the application and transmission of this knowledge on to society. The balance between academic, social, and economic objectives that has marked the development of the ICP has been essential to maintain and enrich this comprehensive profile. This holistic perspective has been possible thanks to the fact that ICP is part the UCR, an institution that combines high academic standards with the search for common good.

The important accomplishments achieved in this area must motivate the generation of new efforts to guarantee continuity and growth. On an academic level, the consolidation of the human team at ICP is key, as well as the encouragement of inter- and trans-disciplinary research through alliances with groups of different disciplines in and outside the country. In the social action (extension) level, a topic that has been so far neglected is the follow-up and support to people who have survived snakebites and who have physical or psychological sequelae. The national health system is not offering the needed attention to these people, which causes great individual and social suffering. A bill needs to be drafted, and actions need to be implemented on different levels to attend this aspect of snakebite envenoming. On the antivenom production level, the sustainability of this project needs to be guaranteed, and this will require the consolidation of the human team in charge of this work, as well as by the construction and equipment of a new production plant; this demands efforts to obtain national and international funds to help consolidate what has been achieved so far, combined with the growth in the management and administration of funds generated by the sales of antivenoms or by the projects.

Finally, this experience teaches us that the development of a collective project of this magnitude transcends national borders to help solve the problem in other latitudes. This extension in the international level has kept the comprehensive vision of the project by including research, antivenom production and distribution, human resources qualification, training to prevent and treat envenomings, and establishing cooperation networks with the production and quality control laboratories. In the end, what has guided these efforts is the belief that science and technology must serve to improve the quality of life and, in this case, to reduce the suffering and pain caused by snakebite envenomings.

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