EXOTIC TROPICAL INFECTIONS

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Introduction

Exotic infection should strictly mean infection from another country or that which is at least strange, it can also be defined as a disease in a region that is under a government abolition program or a disease under surveillance.

Exotic infection epidemiologically can be defined as a disease more likely to occur in some components of the target population than others. The “tropical diseases” Web page, of the World Health Organization (WHO) lists eight diseases that occur exclusively in the tropics and states that, for all practical purposes, the description refers to infectious diseases that proliferate in hot and humid weather conditions. Some of these diseases are caused by protozoa, such as malaria, leishmaniasis, Chagas’ disease, and sleeping sickness. Others are caused by worms, including schistosomiasis, onchocerciasis, and lymphatic filariasis while one is viral, dengue fever. The eight WHO tropical diseases are transmitted to humans by various means, but always include a vector that is generally a hematophagous insect. Schistosomiasis has no vector, but rather intermediary hosts such as snails that release in water the infectious forms for humans.

The designation “tropical diseases” was not invented by the WHO and has been part of the medical vocabulary since the 19th century. It arose at no particular date and was gradually consolidated as microorganisms came to be recognized as the causal factors of diseases and had their transmission mechanisms explained. The colonial expansion of England, France, and other minor partners, including the United States, into the Caribbean and the Pacific and African continent, unfolded a new world full of utilizable riches, but also of unknown or unwanted diseases. Since most of the new colonies were located in the tropics, these curious and exotic diseases were said to be “tropical.” These diseases occur in countries located between the Tropic of Cancer and the Tropic of Capricorn, that is, between latitudes 27° 23’ north and south. Exceptions are the

Middle and Eastern countries whose underdevelopment and the consequent poverty of the tropical population, have a role to play as well.

Aware of this fact, agencies such as UNICEF, the World Bank, and the WHO launched the Special Program for Research and Training in Tropical Diseases (TDR) thirty years ago, which focused on infectious diseases that disproportionately afflict the “poor and outcast populations” of the world. The TDR immediately added tuberculosis and leprosy to the WHO’s list of classical tropical diseases; others were included at various times in the Neglected Tropical Diseases list (NTD): Trachoma, Buruli ulcer, Dracunculiasis, Dengue fever, and Yaws. The list currently contains fourteen neglected tropical diseases and, paradoxically, this number tends to grow as the health conditions of underdeveloped populations improve. This is because only one of these diseases (dracunculiasis) is on the verge of eradication, whereas, the others are ignored until now because of ailments that are seen as more important and have gained visibility in the world sanitation scenario. This has led to the phenomena of emerging and reemerging diseases. These exotic tropical infections are discussed below:

African Trypanosomiasis

African trypanosomiasis, or sleeping sickness, the prototypical tropical disease, is caused by two subspecies of the large group *Trypanosoma brucei*, both of which are specific to humans. The disease exhibits a certain clinical polymorphism, but in the major and more serious form, after a long period of subclinical silence, the central nervous system becomes severely compromised and paralysis, lethargy, progressive inability to think clearly, and death eventually set in. Its initial name, “Negro lethargy”, was changed to “sleeping sickness” as white settlers increasingly contracted it. The disease is now treatable, but treatment is expensive and difficult to administer.

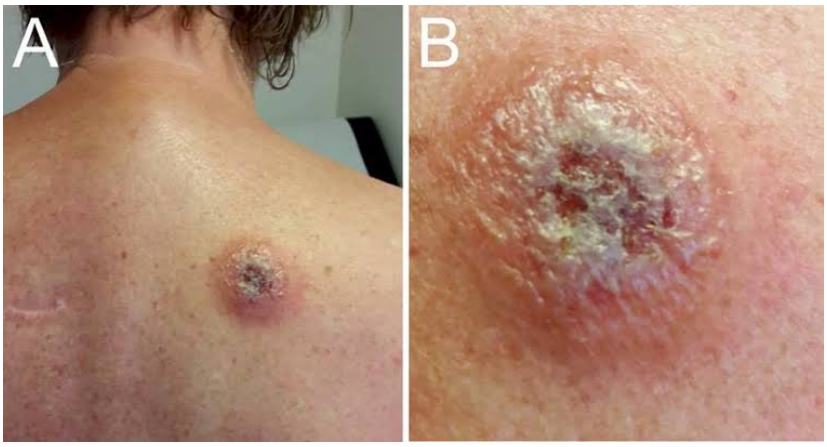

Fig 1: Trypanosomal chancre

In the 19th and 20th centuries, millions of Africans fell victim to it (in 1990, an estimated 300,000 to 500,000 people were infected). The disease takes the form of peripatetic epidemic outbreaks and never occurred outside Africa – it has never been reported anywhere else in the world, whether in the tropics or not. Trypanosomiasis is present over a large belt of African territory, home to approximately 70 million people, extending from the Indian Ocean to the Atlantic, and from the Sahara Desert to the Kalahari, sparing only the north and south edges of the continent. Why is this so? Because the disease is transmitted by a voracious hematophagous fly that lives and proliferates only within those geographical limits. This area is known as the "tsetse belt", roughly between latitudes 20° N and 20° S. There are many tsetse species (genus Glossina) that disseminate different trypanosomes among wild mammals, reptiles, and birds. This becomes economically important, as they can transmit diseases among domestic animals: bovines, ovines, caprines, and equines. Pigs are a preferred victim of the tsetse and also harbor trypanosomes, including human trypanosomes. The human trypanosomes – *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* – is transmitted by tsetse flies from the Palpalis and Morsitans groups, respectively. The Palpalis glossinas proliferate in ancillary woods or shrublands near deposits of water and normally feed on the blood of large reptiles, such as crocodiles; the Morsitans glossinas prefer the savannas and preferably bite wild ruminants. But neither fly is found outside the tsetse belt. Despite the intense slave traffic, neither glossinas nor African trypanosomiasis settled in the New World. Numerous other flies did, however, including the common housefly and the blowfly; but the tsetse never did. Nor did it

expand to the East, nevertheless the long-established trade routes between Africa, India, and the Middle East. The absolute geographic authenticity to Africa of the Glossina explains the tropical fate of sleeping sickness, which is truly a tropical disease – or rather, a strictly African one.

Onchocerciasis

Onchocerciasis is another disease authentic to Africa, but not as intensely so. This fundamentally tropical disease is caused by a nematode, *Onchocerca volvulus*, found in the human dermis, where small male worms (approximately 4 cm) and generous female worms (approximately 50 cm) wind and coil and form skeins that become nodules or dermal swellings that round up like tumors, not always suppurative but always unsightly. The nodules show a marked preference for exposed parts of the skin, especially the face and the scalp, but in naked or seminude populations these nodules (or onchocercoma) can be found everywhere in the body. The worms reproduce in the recesses of the dermis, where the female hatch larvae called microfilariae (approximately 0.5 cm) which moves about subcutaneously and can reach the humor of the eye chamber, cornea, and retina, causing inflammatory reactions that often lead to blindness. In Equatorial Africa, nearly 18 million people harbor the onchocerca worms – 250,000 of them already blind. So great is the suffering, but also the human cohesion involving the disease that the gardens of the WHO in Geneva exhibit a full-size sculpture of a child leading a blind, onchocercotic old man. Indeed, so great is the suffering and the commonality that the pharmaceutical company that manufactures Ivermectin, the active drug against filariae, decided to donate the drug, free of charge, to anti-onchocerciasis programs. Onchocerciasis is also known as river blindness because it is constrained to the populations living near the clear water rivers and streams in whose currents the disease's vectors breed. These are flies of the genus *Simulium*, the black flies of the English, or the popular barracuda of Brazil: the filariae that the flies ingest along with the blood from the patients migrate toward the proboscis, where they change into larvae ready to infect new individuals. Brought by migrant slaves and others, the disease traveled from Africa to the New World, where it found permissive black flies and prospered in the equatorial and supra-equatorial regions of Ecuador, Colombia,

Venezuela, Central America, and southern Mexico. In Brazil, it is restricted to the native and indigenous populations of the Amazon region, particularly the state of Roraima. In the New World, the disease affects no more than a few thousand people and, in general, does not lead to blindness, probably because the filariae on this side of the Atlantic have less affinity for the retina and cornea. Considering the enormous population, broad distribution, and rapaciousness of Brazilian black flies, it is strange that the disease does not occur more often and that it is absent from the northeast to the south of the country, where the barracudas abound and where slave traffic used to thrive.

Could onchocerciasis be a specifically equatorial disease, that is, a subtype of tropical disease? Perhaps the temperature and humidity of the equatorial regions of Africa and the New World are the only climatic factors that allow the development of filariae in black flies – or perhaps black flies capable of transmitting the disease can only proliferate in these regions. Be as it may, onchocerciasis is, and has always been, a disease restricted to the tropics, emphasizing the bio-geographic fatalism of tropical diseases.

Lymphatic Filariasis

Lymphatic filariasis is equally constrained to the tropics. These are caused by the nematode worms *Wuchereria bancrofti*, found all over the tropical world, and *Brugya malayi*, found only in Southeast Asia. The males are always small (approximately 4 cm), the females corpulent (approximately 9 cm), and they live and mate in the lymphatic nodes of men and women (and of no other animal species). The females hatch microfilariae larvae that enter the bloodstream. The worms can become quite numerous after sequential infections and can then occlude the lymphatic vessels, leading to the accrual of lymph upstream.

When lymphatic drainage is compromised, ingurgitation of the compromised regions follows (usually the lower members and the scrotum), generating the so-called elephantiasis. Filariasis has been reported in the upper Nile since time immemorial and the statue of at least one pharaoh shows signs of elephantiasis of the leg. Extremely inflated scrota are commonplace both in African statuettes 1,500 years old and in contemporary patients.

Fig 2: Lymphatic Filariasis (Credit: Department of clinical microbiology and parasitology irrua specialist teaching hospital irrua edo state Nigeria)

More than 120 million people are infected by filariae around the world, including approximately 50,000 in Brazil. Nearly 40 million individuals have been debilitated or deformed by elephantiasis. It is estimated that more than 1 billion people are at risk of contracting one of the filariae, which are transmitted from human to human by the pervasive and diverse ordinary mosquitoes. Dengue fever's Aedes and malaria's Anopheles can also transmit filariae, but these insects are not the most important ones. Arguably, the most important of all is the common mosquito of the genus *Culex*. The microfilariae that are sucked with the blood of an infected individual develop inside the mosquitoes and are transmitted to other probable patients. However, multiple infections are required for the disease to manifest. The agents used to treat filariasis, the same as the ones for onchocerciasis, are donated free of charge by the laboratories that produce them – a rare but dignifying example of the pharmaceutical industry. Filariasis is under pressure from intensive global and local control programs, and its incidence tends to diminish around the world. But one fact draws attention: the vectors for filariasis, the common mosquitoes, are everywhere and bite all types of people – nobles and paupers, pariahs and popes – since time immemorial, but filariasis have only been reported in the tropics.

Schistosomiases

The two major schistosomiases afflict 200 million people, half of them in Africa, the remainder in the Middle East and South America, especially in Brazil and Venezuela. Three milder and less important schistosomiases are restricted to southeast Asia, including China and Japan. They are all caused by worms and conveyed by snails. The adult worms live in the intestinal or vesical veins, and their eggs are eliminated, respectively, through the feces and urine of the patients. *Schistosoma mansoni* lives in the intestinal veins (portal system) and the eggs that do not reach the intestine may reflow into the liver, causing foci of inflammation that heal as fibrosis, leading eventually to cirrhosis and its serious consequences. *Schistosoma haematobium* lives in the veins of the vesical plexus and its eggs may cause fibrosis and minor urinary hemorrhages; if these become chronic, the consequence can be anemias of variable clinical severity. The Mansoni schistosomiasis of Brazil was imported from Africa at the time of the slave trade, established in the east and northeast, with scattered foci all over the country. In the 1950s, the disease afflicted 6 million Brazilians. Haematobic schistosomiasis never managed to set foot in Brazil, despite the slave trade, and currently prevails in equatorial and subequatorial Africa, with ramifications in the Nile River valley, Algeria, Tunisia, and Saudi Arabia. Larvae (miracidia) emerge from eggs that the worms deposit in repositories of fresh water, and invade snails of the genus *Biomphalaria* in Brazil and Africa, and the genus *Bulinus* in Africa. The larvae multiply within the snails and generate other larvae (cercariae), which then abandon their snail and go swimming after the humans (who use this infected repository of water for their basic needs, especially in Africa). Schistosoma haematobium never gained a foothold in the New World, because it never adapted to the *Biomphalaria*, and requires certain species of *Bulinus* exclusively to proliferate – which, in turn, did not adapt to the Americas. *Schistosoma mansoni* was brought from Africa by the slaves and found in Brazil numerous species of *Biomphalaria* in which to proliferate. The schistosomiases (and, in particular, hematobic schistosomiasis) are a convincing example of geographic stoicism: despite the intense traffic past and present between every geographic region, they refuse to leave Africa – at most, they made some small incursions into

Madagascar and the Near east.

Leishmaniases

The leishmaniases are caused by different species of *Leishmania*, which are intracellular protozoa of humans and domestic and wild animals. The cutaneous leishmaniases found in Amazonia are an unquestionable example of the “tropical curse”. Other leishmaniases occur not only in tropical regions but also somewhat further north, including the Mediterranean countries. Strictly speaking, they should not qualify as tropical, or as diseases of outcast populations, because they occur in many regions of the developed world, such as the Iberian Peninsula, Italy, Greece, and Turkey. The most serious leishmaniasis, caused by *Leishmania donovani*, is the so-called visceral leishmaniasis (or kala-azar, or black fever), reported for the first time in India, but present also in Africa and Latin America. Approximately 500,000 new cases are reported each year. The disease, with its chronic and debilitating development, results from the proliferation of leishmania in the macrophages of the spleen, liver, and bone marrow. It is difficult to diagnose and, if untreated, fatal. India, Brazil, Ethiopia, and Sudan, as well as the north African countries, are the greatest victims. It was a major health issue in China but is now under control there. In the present decade, Brazil has been reporting 3,000 new cases per year, a number that is not so frightening when compared to the 600,000 new cases of malaria or 100,000 of tuberculosis. Other leishmania’s cause cutaneous or muco-cutaneous ulcerations that are unattractive and deforming, but rarely fatal. Among these are the Old World leishmania’s, particularly those from the East, including some as benign as *Leishmania tropica*, and dozens of New World species, notably *Leishmania braziliensis*, identified by Gaspar Viana, which is aggressive and deforming on account of the lesions to the buccal and pharyngeal mucosa’s, sometimes leading to the destruction of the nasal cartilage. According to WHO estimates, the world sees 1 million new cases per year, 30 thousand of them in Brazil. But the New World leishmaniases are not post-Colombian, that is, they were not imported from the Old World; on the contrary, they are endemic and probably prevailed here since the arrival of Homo sapiens 30,000 to 10,000 years ago, judging from the typical lesions found in Inca mummies and in statuettes dated more than 2,000

B.C.Leishmania's are transmitted to humans by a group of minuscule flies, known as sand flies and by many other regional names. They all belong to the *Phlebotomidae* family. In the Old World, they belong to the genus *Phlebotomus*; in the New, to the genus *Lutzomyia*. The sand flies are insatiable hematophagous and feed on all sorts of vertebrates: amphibians, reptiles, birds, and mammals, disseminating trypanosomes and leishmania's among them. Different species of sand flies seek out human leishmania's in different hosts: the visceral leishmania's, especially in infected humans or dogs.

Actually, in most of the world, sick humans are the reservoir of visceral leishmaniasis, but in Brazil dogs still play a very important role as reservoirs. In Brazilian cutaneous leishmaniases, the main reservoirs are the abundant wild rodents, abundant in the Amazon Forest and recently deforested areas. Visceral leishmaniasis occurs in houses or near houses but is liable to control, as attested by China, where mass treatment, spraying with insecticides, and the elimination of dogs reduced the prevalence of kala-azar in the 1950s, from 500,000 cases to no more than 200. On the other hand, cutaneous-mucous leishmaniases, particularly those in the Amazon region, seem to be more difficult, if not impossible, to control. The Lutzomyia's are to be found everywhere in the forest; day and night they bite their preferred victims, the omnipresent rodents who are unending reservoirs of leishmania's. When humans interfere in this cycle, in this veritable ocean of Lutzomyia's and leishmania's, they run the risk of being bitten by one and infected by the other. The risk is greater in recently settled areas where deforestation and the flight of rodents have turned humans into a more important than usual source of food for the Lutzomyia's. This cannot be avoided; it is the unavoidable curse of the rainforest. It is not possible to spray the entire forest or exterminate all rodents and other reservoirs. Such destruction would cause more harm than the disease itself. One must wait for an effective vaccine, which is still not even on the horizon, to neutralize this type of tropical voodoo. Combined, "poverty" and "tropics", more than any of these factors alone, have always been cruel to humankind, conspiring to turn the lives of millions into a living hell. This situation is clearly expressed in an index – the Disability Adjusted Life Years (DALY), a time-based measure conceived by

the WHO to assess a disease's burden that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. In short, the Daly measures the life lost to premature deaths or debilitating sickness by the global or regional population (as desired). One Daly unit equals one year of life. For "tropical diseases", the DALY indices listed by the WHO are: malaria, 46.5 million years lost by humankind; tuberculosis, 35 million; filariasis, 5.8 million; leishmaniases, 2 million; schistosomiases, 1.7 million; sleeping sickness, 1.5 million; Chagas' disease, 667 thousand; dengue fever, 616 thousand; onchocerciasis, 484 thousand; leprosy, 199 thousand.

Concerning the number of deaths per year, the situation is equally regrettable: tuberculosis, 1.5 million; malaria, 1.2 million; visceral leishmaniasis, 51 thousand; sleeping sickness, 48 thousand; dengue fever, 19 thousand, schistosomiases, 15 thousand; Chagas' disease, 14 thousand. Finally, whereas life expectancy in Japan is approximately 8 decades, in many countries in tropical Africa it is no more than 4 decades. But what is becoming increasingly clear is that the "tropical fate" can be significantly reversed by economic and sanitary development in general, or by the timely allocation of specific resources.

Chagas' Disease

The control of American trypanosomiasis, or Chagas' disease, in Brazil, is a patent example of how this is possible. Chagas' disease is caused by *Trypanosoma cruzi*, which only occurs in the New World, and has been separated from its sleeping sickness-causing relatives for at least 100 million years, ever since Africa and South America disjoined. The concomitant separation of the faunas and floras also underlined the continental disjunction of trypanosomes and vectors. The ancestors of the glossinas (tsetses) survived in Africa, while the ancestors of triatomine bugs colonized South America. One could not find a more clear-cut case of tropical "biogeographic fate". More fortunate Europe inherited neither of these ancestors. The triatomine bugs, commonly known as "barbeiros" in Brazil, are hematophagous Hemiptera with species distributed in three main genera – *Triatoma, Panstrongylus, and Rhodnius* – that

proliferate in different biomes in North, South, and Central America. Species of barbeiros, also called kissing bugs, can be found both in burrows or caves and in treetops, especially in palm trees. They feed on the blood of a wide range of mammals, from armadillos to primates, and are generalists concerning their victims.

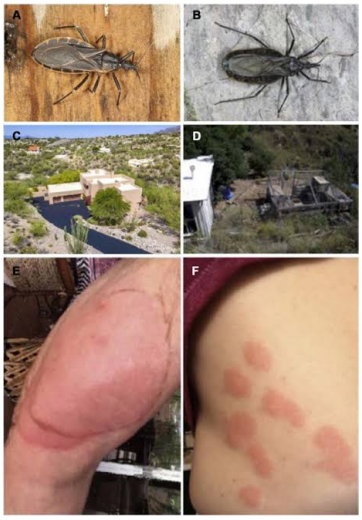

Fig 3: Chagas Disease (Photo credit: sciencedirect.com)

Marsupials and armadillos must have been the original hosts of T. cruzi and, thanks to the hematophagous promiscuity of the kissing bugs, they must have then disseminated to the various orders of mammals in South and, later, North America. Humans were probably included in the promiscuous list of victims since their arrival in the Americas, some 30,000 to 10,000 years ago, but only became regular and constant feeders of the kissing bugs when they brought them home and domesticated them together with mammals infected by T. cruzi. It is surmised that this is what happened to the pre-Colombian populations of the Andes, who raised guinea pigs (Cavia spp) as foodstuff, whom the kissing bugs (Triatoma spp) also fed on. From then on, the kissing bugs, particularly *Triatoma infestans*, adapted so well to human households and their inhabitants (humans, dogs, and other animals) that they started to prefer humans for their bloody banquets and to live and procreate in the so-called house of man. They loved the long, dark, and hot tunnels of the wattle and daub houses that were found all over Brazil. At night, *T. infestans* appeared from these tunnels to bite humans, preferably in the tender palpebral region or anywhere in the face – thus the Brazilian name Barberio [barber] or kissing bug. While they munch away, these bugs defecate on the very face that feeds them. In their feces are the infectious trypanosomes that travel

along the orifice of the bite and reach the underlying cells, which they invade and where they multiply. Cells crammed with trypanosomes eventually burst, releasing them into the bloodstream, whereby they reach other cells. The kissing bugs become infected by ingesting blood with circulating trypanosomes.

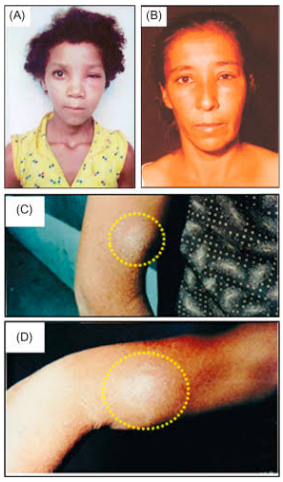

Fig 4: Manifestation of Chagas Diseases (Credit: sciencedirect.com)

In humans, the trypanosomes show a predilection for the neurons of the autonomous nervous systems and the muscle cells of the heart. The progressive destruction of these cells is responsible for the symptoms of the chronic stage of the disease: lesions to the heart's motor systems, with arrhythmias, blockages, and even cardiac arrest; lesions to the fibers of the heart, diminishing its contractility and leading to heart failure; lesions to the nerve cells of the stomach's sphincters and of the sigmoid flexure, which progressive occlusion and enlargement of the esophagus and the colon. Death can occur already in the acute phase or at any moment of the chronic phase, but the disease generally extends for several years. Treatment with medication is complicated, not very efficient in the chronic phase, and has many risks and side effects.

Chagas' disease and malaria were the most serious endemic diseases in Brazil. Until the 1970s, approximately 20 million Brazilians were infected by *T. cruzi* and until 1980 there were at least 120,000 new cases of the disease each year. By then, however, it was already known that controlling the disease was possible because the state of São Paulo had reduced the number of new cases by spraying insecticide in households

infested by the kissing bugs. In the 1980s, Argentina, Brazil, Chile, Paraguay, Uruguay, and the Pan-American Health Organization (OPAS) launched an intensive program to fight the kissing bugs: The Southern Cone Chagas Initiative. The program was an absolute success. In Brazil, after only a few years of systematic and well-planned spraying, the number of new cases fell practically to zero.

Chagas' disease transmitted by domestic kissing bugs (Triatoma and Pastrongylus) proved to be controllable. A few sporadic cases of household transmission still occur, but these are only residual foci of a disease on the verge of extinction as a result of permanent health surveillance. Unfortunately, many Latin American countries did not carry out similar programs. Bolivia, for example, still has an incidence of more than 80,000 new cases per year. In countries north of the Equator, the main transmitters of *T. cruzi* to humans and dogs are the kissing bugs of the genus *Rhodnius* and the domestic *Triatoma dimidiata*. Strategies to control transmission, although different from those adopted by the Southern Cone countries, are possible, and Central American countries have organized themselves to implement their regional program: The Central America Chagas Initiative. In Brazil, as elsewhere, including the United States, *T. cruzi* is still present in mammals and kissing bugs in the wild, and neither the partners nor their partnership will be extinguished in the next million years. Thus, new foci of Chagas' disease can emerge at any moment and have indeed emerged in small communities densely populated by infected mammals and kissing bugs. Amazonia is an advantageous scenario for such events.

The prevalence of Chagas infection has been caused by the ingestion of fruit juices (especially assai) and of sugar cane accidentally ground together with kissing bugs infected with trypanosomes of wild animals. These outbreaks of oral infection usually strike dozens of people at once but are always limited. Both types of episodes can occur at any moment, but Chagas' disease as a nationwide scourge is something that will never happen again. However, since the tropical biogeographic fate of kissing bugs and trypanosomes has not changed and both villains are still everywhere and scot-free, we can't completely say there won't be another nationwide scourge of the disease. Notwithstanding, development has neutralized the biogeographic fatalism and

sanitation has become a reality in Brazil. The number of mud huts has fallen and those that remain are regularly sprayed with insecticides provided by the health authorities. Financial resources have been made available and health surveillance is permanent. Undeniably, development is the best antidote to tropical fate.

Other Tropical Diseases

Yaws or frambesia is a skin treponematosis and, like syphilis, can be easily treated with penicillin; the disease only exists because afflicted populations have no access to health services. Buruli ulcer, rare or undiagnosed in the New World, comes from a mycobacterium that causes extensive cutaneous lesions, usually in the lower members, in populations living near rivers, or in marshy areas.

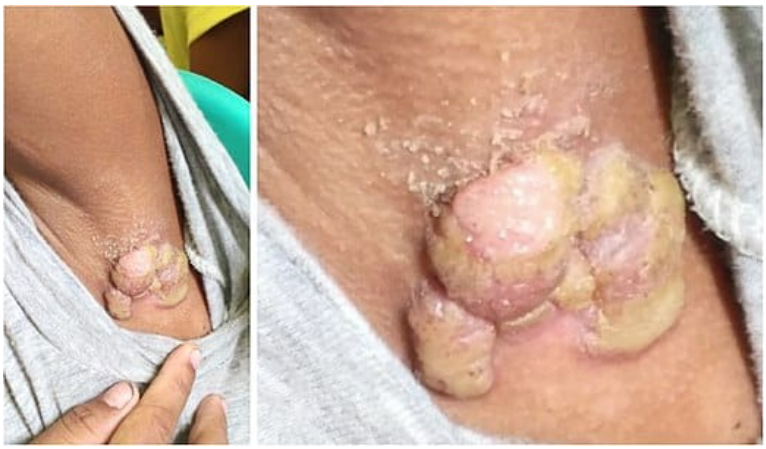

Fig 5: Yaws ulcer in the axilla (Photo credit: Wikipedia)

Trachoma, a chlamydial eye infection, occurs only sporadically in Brazil but victimizes 80 million poor people around the world, 6 million of which have been made blind. Not to mention the intestinal verminoses, less alarming but still prevalent in underdeveloped countries, side by side with cholera and generic child diarrheas. All and any of these could be called either tropical diseases or diseases of underdevelopment. The eclectic name “neglected diseases”, adopted by the WHO, comprises all of them, without distinguishing the tropics as a causal factor.

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