The History of the Dissemination of Microorganisms

Stefan Cunha Ujvari



[Bird flu – health agents dressed in protective clothing, masks and goggles inspect a chicken farm in the Da Nang region of Vietnam]

he term "globalization of microorganisms has gained evidence in recent years. The population has realized that, with air travel, an infected individual can take a round-the-world trip in a short span of time. This means that epidemics can disseminate throughout the globe with greater ease. The Asian pneumonia outbreak in 2003 spread from Southeast Asia into Europe and America. The world held its breath for fear of a globalized epidemic. Print and TV news spared no column inches or air-time in covering the epidemic. Today, the news is focused on "bird flu". We are expecting another global flu pandemic at any minute, something on the level of the "Spanish flu" outbreak of 1918. Today, an epidemic could spread across the globe with astonishing speed. However, we could tell another tale of epidemic globalization that has been unfolding for a lot longer, and practically unnoticed. It began with our emergence in Africa and continues today, depending on human locomotion for its slow

and progressive advance. It the beginning, its steps were tentative, but in recent decades, it has burst into a stride.

Modern man's earliest hominine ancestors appeared some seven million years ago. Science identifies Africa as the centre of the advent of the first bipeds. The earliest hominines split from the originary ancestral line it shared with the chimpanzee, but studies of genetic material of microorganisms show that they were not alone. Ancestral labial and genital herpes took the leap with them, and accompanied the various subsequent species as they evolved and died off. They thrived and evolved among the Australopithecines, in *Homo erectus, Homo ergaster, Homo habilis*, and on to modern African man (Sharp 2002; Leal & Zanotto, 2000). The erect, bipedal posture of the hominines kept labial and genital herpes geographically isolated, allowing them to mutate into the distinct genetic strains we have today (Gentry et al., 1988). Calculations based on the genetic differences between these two types of herpes traced them back to an initial viral form that surged roughly eight million years ago, most likely with the emergence of the first bipedal hosts (ibidem).

That ancestral animal common to both man and the chimpanzee carried a herpes virus that it passed on to the chimp line as well as the human, with modern chimpanzees presenting strains of labial and genital herpes genetically very similar to our own (Lacoste et al., 2005; Luebeke et al., 2006; Davison et al., 2003).

It is highly likely that the human papillomavirus (HPV) followed this same course. We find viruses similar to HPV in primates, which would suggest its existence in man and the chimp's common ancestor (Ostrow et al., 1990; Reszka et al., 1991; Chan et al., 1997).

Ancestral humans in Africa contracted parasites from the herbivorous animals they began to hunt on the African savannah. Among these were the initial forms of tenia. Genetic studies reveal a similarity between the tenia that affect humans today and those found in African felines, canines and hyenas (Hoberg et al., 2001). This would suggest that we did not contract tenia from the domestication of swine, but that they were already present in man on African soil and transferred to pigs and cattle with the advent of husbandry.

Forms of the bacteria that cause tuberculosis, discovered in Djibouti, reveal their genetic ancientness and were probably the precursors of today's *Mycobacterium tuberculosis* (Fabre et al., 2004). This would suggest that tuberculosis already assailed human ancestors as remote as *Homo erectus*. *M. bovis*, which occurs in cows, was believed to have been transferred to man with the domestication of cattle. However, this theory collapsed with the discovery of the Djibouti bacteria and comparative studies of the genetic sequences of mycobacteria, which place *M. bovis* as one of the latest strains to evolve (Brosch et al., 2002).

Intestinal parasites acquired through contaminated water and foods are known to have troubled the first *Homo sapiens*.

So we were born infectious agents and acquired new infections while still on African soil. We were already stocked and ready to begin the globalization of microorganisms when we left Africa to conquer the planet.

Mankind's African diaspora took a little under a hundred thousand years. Out of Africa, we moved into the Middle East, up into Europe and on into Asia. Migrations to the Asian hinterlands and coast took us out into the Far East. Straying humans colonized Oceania and its islands while others, moving into the tip of Northeast Asia, reached the American shore and headed south. Soon, man was to be found on all the continents of the Earth.

Genetic comparisons of microorganisms in native populations reveal the globalization of some infectious agents by the first humans to leave Africa. HPV and *Helicobarter pylori* present in native Amerindians are genetically descended from those found in Asian populations, which, in turn, descended from strains found in the Middle East, themselves a mutation of earlier African strains. The human hunter-gatherers that went on to people the planet took their bacteria and viruses with them (Wirth et al., 2005; Ho et al., 1993; Falush et al., 2003; Linz et al., 2007).

Indigenous mummies from the Atacama Desert in Peru show signs of tuberculosis. Bacterial DNA was found in the lungs of mummified natives. Homo sapiens carried the tuberculosis bacteria with it when it left Africa and it spread it to the four corners of the earth.

Fossilized feces (coprolites) in the intestines of Amerindian mummies prove the presence of a range of intestinal parasites carried there by the first humans migrating into the Americas (Bouchet et al., 2003b). One of these sheds particular light on the route by which human migrants reached America. For years it was believed that mankind arrived in America across the Berring Straight, when, during the last Ice Age, a drop in sea level exposed a narrow land bridge across which humans on the farthermost tip of the east could enter the continent from the north. However, traces of the parasite Ancylostomo duodenalis has been found in coprolites of American Indians. This parasite lays its eggs on the ground, where larvae develop and penetrate the skin of new hosts to perpetuate the cycle. However, these eggs require reasonably warm, moist soils in order to hatch, characteristics most definitely lacking in the frozen ground of Ice-Age Beringia. This finding adds credence to the newer theory that the first humans to reach the Americas arrived in vessels over sea, where the coastal soils would have been more suitable for the dissemination of Ancylostomo duodenalis (Montenegro et al., 2006).

This first wave of globalized microorganisms was characterized by a low mortality rate and slow, chronic illness, which stands perfectly to reason, considering that human populations at the time were small and highly lethal infectious agents would have wiped out their own vectors.

Once scattered across the globe, mankind worked a revolution in alimentation. The advent of agriculture and domesticated livestock took place within the last ten thousand years. Man gave up his nomadic ways and settled down. Irrigated areas and wetlands spread along with agricultural practices. Reservoirs and irrigation canals began to appear around villages, providing ideal breeding grounds for malaria-carrying mosquitoes and the freshwater snails that serve as vectors for schistosomiasis. Malaria accompanied the population increase triggered by a greater supply of food produced through agriculture, thriving along the Mediterranean shore and the coasts of Africa, the Middle East and Asia. Marks left on mummies testify to the fact that schistosomiasis followed humans throughout Africa and Asia.

Husbandry exposed us to the viruses present in animals. Mutating bovine viruses gave rise to measles, which originated in Asia. In cattle, the virus causes the bovine plague, a lethal disease that was brought there by European herds. Bovine plague tormented European cattle-ranchers in the 17th and 18th Centuries. During the colonization of Africa, the Italians and English brought cattle to the horn of Africa, and the bovine plague virus along with them. The disease spread like wildfire throughout Africa, wiping whole populations of antelope and buffalo, zebra, giraffe, gazelle and cattle off the African map. (De Salle, s.d.) Only today are we coming close to ridding the continent of this pest.

Another mutating animal virus infected man and became smallpox. The camel is one of the prime suspects as transmitter, as it suffers from a virus genetically very similar to smallpox (Gubser & Smith, 2002). Another suspect is a small Asian gerbil that would have been abundant in the bush surrounding the earliest Asian cities and which is known to host a virus genetically akin to smallpox.

Now, with the huge population growth agriculture enabled, we begin to see the first fierce epidemics and outbreaks of lethal viruses like smallpox.

Globalization continued with the Romans. The Roman Empire extended its borders to North Africa, the Middle East and Britain. All roads led to Rome. The circulation of traders and legionnaires aboard Mediterranean ships and paved roads brought smallpox and measles to Europe from the Middle East and Africa, causing terrible outbreaks in Rome.

Trade in the Middle Ages kept up the globalizing momentum. The bacteria that caused the Black Death came to Europe aboard Genoan trade ships from the Black Sea in 1348. It took the plague only two years to engulf the continent and kill off as much as a third of the European population. The bacteria lingered, triggering sporadic bouts in the cities. The Crusades, followed by trade routes to and from the Middle East intensified the arrival of leprosy in Europe. The genetic make-up of this disease can be traced to the Middle East, India and the vicinity of Egypt. The European strain descended from these.

Viruses, bacteria and parasites spreading throughout Europe ran up against a natural barrier in the Atlantic Ocean, but man was to provide a helping hand in the form of long-range shipping, initially with the intensification of trade and exploration along the west coast of Africa. According to the genetic trail, it



The outbreak of foot-and-mouth disease in Britain – To curb the spread, animals are slaughtered and burned at the Prestwick Hill farm near Newcastle, England

must have been aboard one of these ships that the bacterium that causes leprosy arrived on the African coast (Monot et al., 2005). In exchange, however, the European travelers went home with schistosomiasis. Eggs of this parasite can be found in 15th and 16th-century French latrines and cesspits (Bouchet et al., 2003 a). Nevertheless, none of that compares with the discovery of the Americas.

European ships brought smallpox, measles and the flu to native Amerindians. These three diseases ravaged the natives along the coast and advanced inland. Smallpox decimated the Aztecs and facilitated their conquest by Cortez. It also swept the Inca Empire with measles, paving the way for its subjugation by Pizarro. Influenza, previously unknown to the indigenous peoples, triggered one of the most devastating epidemics, sparking a series of Spanish flu-like outbreaks among the tribes. An estimated 90% of these Amerindian populations were wiped out by this trident of disease from Europe (Mann, 2005).

However, the Amerindians responded in kind. The origin of syphilis remained a matter of debate for many years. Did it already exist in Europe before transatlantic travel or was it brought back to Europe from the Americas? Traces of the disease in pre-Columbian American ossuaries testify to the presence of the disease during this period (Rothschild & Rothschild et al., 2000), which would mean it was brought back to Europe on ships. However, even stronger genetic evidence was to confirm the American source.

In the early 20th Century, Canadian doctors discovered a strange skin disease in indians in the Guianas. The malady was caused by the same bacterium that causes Yaws disease, a cousin of syphilis. Yaws was largely controlled and practically eradicated among indigenous populations by a World Health Organization campaign in the early second half of the 20th Century. However, the clinical manifestation of this strange disease among indians in the Guianas led the doctors to send samples for genetic analysis. The results revealed a strain of bacterium different to the common form of Yaws and genetically closer to syphilis. A mutating American bacterium had turned Yaws into syphilis; this is the most likely explanation for the origin of the venereal disease and proof that it traveled originally from America to Europe, and from there to the rest of the globe.

America was colonized by the Europeans and their microorganisms as well. Tuberculosis, rife in Europe during the centuries succeeding the Discovery, found its way to the colonies. The strains of this disease still encountered in the Caribbean are descended from the European bacterium from the time of colonization and engendered a second wave of tuberculosis to sweep the Americas.

Another continent harnessed to the task of Europe's conquest of America was Africa, which began to export slave labor to the colony in the 16th Century. Though the number of slave ships bound for America was low at first, the trade swelled over the coming centuries, proving an efficient vector for microorganisms. Water barrels aboard slave ships were probably responsible for bringing the

mosquito that transmits yellow fever to the New World. The first recorded outbreak of the disease was on the British colony of Barbados in the 17th Century. Caribbean vessels helped spread the virus to the rest of the islands and to the nations of Central America, where it found mosquito populations capable of reproducing the disease. Hence it took a firm hold in Central America and began to make incursions into North America and the northern territories of South America, completing the manmade globalization of yellow fever, hitherto an exclusively African virus.

Summer after summer, outbreaks of the disease tormented the Caribbean and it eventually reached the port of New Orleans. Mankind would continue to propagate the spread. In late 1849, a ship brought the virus from the southern states of the USA to the cities of Salvador and Rio de Janeiro, with the Rio epidemic being particularly severe. A number of theories were devised to account for the Brazilian epidemic: was it Divine punishment for the nation's reluctance to abolish slavery? This seemed to make sense, seen as the vast majority of the victims were of European descent, while the Negroes appeared relatively unaffected. This Divine justice was meted out to the guilty while sparing the innocent. Of course, the real reason for the discrepancy was that most of the slaves had been born in Africa and had contracted yellow fever during childhood, so they were already immunized. A rival to the Divine Justice argument was the warning from Brazilian doctors that there was a real risk of the slave ships bringing diseases to the country. Both sides of the concern contributed to the eventual abolition of the slave trade in both law and practice.

Yellow fever found dense human populations and a proliferation of mosquitoes in wetland areas around Brazilian cities. Rio de Janeiro was an ideal place for the virus to spend the rest of the 19th Century. It was only at the beginning of the 20th Century, with certainty that mosquitoes were indeed responsible for transmitting the virus, that steps were taken to combat the disease through campaigns to destroy the insect's breeding grounds. This ordeal along the Brazilian coast will not sound unfamiliar. A little over a century later, a virus transmitted by the mosquito *Aedes aegypti* caused a flurry of yellow fever epidemics during successive summers. The health authorities launched annual campaigns to prevent the collection of stagnant pools of rainwater in which the mosquito lays its eggs.

Malaria was another disease proliferated by man. The parasite was endemic to the Mediterranean and African coast, but European and African ships brought the vector mosquitoes and/or infected individuals to America, where it raged through coastal towns and settlements before penetrating into the forest. Though it would be beaten back by public health campaigns, malaria nonetheless found refuge in the Brazilian jungle, were it has remained ever since.

The slave ships brought yet another colonizer to the Americas – the schistosomiasis parasite. Brazilian *schistossoma mansoni* derived from Africa, but the DNA traced the parasite back to Asia (Lockyer et al., 2003). The parasite

found its way from Asia to human populations in Africa during Antiquity. Manmade irrigation channels and dams helped proliferate freshwater snails that transmit the disease in the large rivers of Africa and Asia. Samples of species of the parasite that affect the urinary tract have been found encrusted into mummies from Ancient Egypt. The farmers of Antiquity walked barefoot in waters rife with the parasite.

It is believed that African slaves infected with the parasite brought it to Brazil, where their feces released its eggs into lakes, rivers and reservoirs. They found a suitable vector in the American snail. The disease came through the main gateway for incoming slaves – the Northeast. In the centuries that followed, human locomotion introduced the parasite to the rest of the Brazilian wetlands.

The industrial period in Europe gave rise to new infections hitherto rare in humans. With the Industrial Revolution of the 18th and 19th Centuries, thousands of rural peasants migrated to the cities and towns in search of work in the factories. An army of impoverished laborers was left vulnerable to microorganisms. Children and women submitted to grueling shifts, their immune systems weakened by exhaustion, were easy pickings for bacteria and viruses. Low wages made a proper diet impossible, which further weakened resistance. Malnutrition was rife among the European working class, and high rent crammed whole families into the same small room.

Overcrowding and poverty lay fertile ground for air-borne contagious diseases. The 18th and 19th Centuries were dominated by tuberculosis, whooping cough, diphtheria and scarlet fever. More than half of the children did not live past the age of five. Industrial cities were a hotbed for microorganisms.

The battery of air-borne microorganisms was reinforced by an equally vast array of food and water-borne bacteria and viruses, which thrived in European and American industrial cities, where there was no treated water supply. Latrines and sewage pipes were not to be found in these industrial redoubts, and garbage and waste accumulated in cesspits, barrels and landfills. This dejecta ultimately ended up discharged into the rivers, which were very often the population's sole source of drinking water. Epidemics of diarrhea were very common in these centuries, aggravated by the globalization of the cholera bacteria during the Industrial revolution.

Cholera could spread from its Asian cradle only with the help of the steamships that came with the Industrial Revolution. Swifter ships arrived with carriers of the bacterium. The disease made port in Europe and spread throughout the industrial cities, packed full of vulnerable inhabitants with no basic sanitation. It crossed the Atlantic to America, reaching Brazil in 1850. There were six cholera pandemics throughout the 19th Century. The construction of the Suez Canal shortened the distance between Europe and Asia and served as a shortcut for the cholera bacterium. The European and American working classes now shared the same scourge.

In the last quarter of the 19th Century science discovered that infectious

diseases were caused by bacteria, parasites, fungi and viruses. Despite our best efforts to curb their spread, the 20th Century saw the continued dissemination of infectious diseases.

Viruses genetically similar to the dengue virus have been found in monkeys from the Malaysian peninsula. These are the likely culprits for supplying the virus that was to mutate into human dengue (Wang et al., 2000; Forattini, 2003). Demographic expansion probably brought man into contact with wild monkeys and consequently also with the life cycle of this virus. The virus transferred from monkey to man and began its cycle of infections via mosquitoes in the city environment. Sea traffic would then have disseminated the four strains of the dengue virus to the Asian islands and mainland, as well as to the east - and later west - African coast. From African ports, it set sail for the Americas.

Genetic comparisons of type 3 dengue reveals the course the virus took since it left India and Sri Lanka in the 1960s (Messer et al., 2003). Ships brought DEN-3 to east African ports. It arrived first on the coast of Mozambique, triggering the epidemic of 1984-85. Six years later the virus was raging through Kenya (1991), followed by Somalia (1993). Sea traffic brought the virus to America in 1994, sparking epidemics in Panama and Nicaragua. In the late 90s, the virus spread throughout Central America and made its way south into Brazil and Venezuela in 2001.

In the 1980s, Brazilians had felt the first major dengue epidemics, but noone would have imagined that the virus was here to stay. The 80s was also a time in which another globalized virus was to arrive in Brazil – AIDS.

Chimpanzees from Gabon and Cameroon transmitted the mutating virus to their hunters. The slaughtered bodies and bloodied tissues of these primates were handled by the hunters and traders in the markets of villages and towns, where people came into contact with the animal's blood and the viruses it contained. The invasion and subsequent mutation of this virus in humans gave rise to AIDS in the 1930s (Korber et al., 2000; Salemi et al., 2001). The virus spread among Africans in the 1960s, a time that provided no shortage of opportunity for viral proliferation, given the various wars of independence, civil wars, military coups and guerilla activity, and everything that goes with such turmoil: misery, prostitution, refugee migrations, rape and urban sprawl.

The virus made port at Haiti, from where it spread into the United States of America and globalized through human migrations to reach every continent on the globe.

Bibliography

BOUCHET, F et al. The state of the art of paleoparasitological research in the Old World. *Mem. Inst. Oswaldo Cruz*, v.98 (Suppl. I), p.95-101, 2003a.

_____. Parasite remains in archaeological sites. *Mem. Inst. Oswaldo Cruz*, Rio de Janeiro., v.98 (Suppl.1), p.47-52, 2003b.

BROSCH, R. et al. A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. *Proceedings of the National Academy of Sciences*, v.99, n.6, p.3684-9, 2002.

CHAN, S.-Y. et al. Genomic diversity and evolution of papilomavirus in Rhesus monkeys. *Journal of Virology*, v.71, n.7, p.4938-43, 1997.

DAVISON, A. J. et al. The human cytomegalovirus genome revisited: comparison with the chimpanzee cytomegalovirus genome. *Journal of General Virology*, v.84, p.17-28, 2003.

DeSALLE, R. (Ed.) *Epidemic!: the world of infectious disease*. New York: The New Press; The American Museum of Natural History, s. d.

FABRE, M. et al. High genetic diversity revealed by variable-number tandem repeat genotyping and analysis of hsp65 gene polymorphism in a large collection of *Mycobacterium canettii* strains indicates that the *M. tuberculosis* complex is a recently emerged clone of *M. canettii. Journal of Clinical Microbiology*, v.42, n.7, p.3248-55, 2004.

FALUSH, D. et al. Traces of human migrations in Helicobacter pylori populations. *Science*, v.299, n.5612, p.1582-85, 2003.

FORATTINI, O. P. Epidemiology and phylogenetic relationships of dengue viruses. *Dengue Bulletin – Escola de Saúde Pública da Universidade de São Paulo*, n.27, p.91-4, 2003.

GENTRY,G. A. et al. Sequence analyses of herpesviral enzymes suggest an ancient origin for human sexual behavior. *Proceedings of the National Academy of Sciences*, v.85, p.2658-61,1988.

GUBSER, C.; SMITH, G. L. The sequence of camelpox virus shows it is most closely related to variola virus, the cause of smallpox. *Journal of General Virology*, v.83, p.855-72, 2002.

HO, L. et al. The genetic drift of human papillomavirus type 16 is a means of reconstructing prehistoric viral spread and the movement of ancient human populations. *Journal of Virology*, v.67, n.11, p.6413-23, 1993.

HOBERG, E. P. et al. Out of Africa: origins of the Taenia tapeworms in human. *Proc. R. Soc. Lond. B.*, v.268, p.781-7, 2001.

KORBER, B. et al. Timing the ancestor of the HIV-1 pandemic strains. *Science*, v.288, p.1789-96, 2000.

LACOSTE, V. et al. A novel homologue of Human herpesvirus 6 in chimpanzees. *Journal of General Virology*, v.86, p.2135-40, 2005.

LEAL, E. S.; ZANOTTO, P. M. A. Viral diseases and human evolution. *Mem. Inst. Oswaldo Cruz*, v.95 (Suppl. 1), p.193-200, 2000.

LINZ, B. et al. Na african origin for the intimate association between humans and Helicobacter pylori. *Nature*, v.445, n.7130, p.915-8, 2007.

LOCKYER, A. E. et al. The phylogeny of the schistosomatidae base don three genes with emphasis on the interrelationships of Schistosoma Weinland, 1858. *Parasitology*, v.126, p.203-24, 2003.

LUEBCKE, E. et al. Isolation and characterization of a chimpanzee alphaherpesvirus. *Journal of General Virology*, v.87, n.1, p.11-9, 2006.

MANN, C. C. 1491: New revelations of the Americas before Columbus. New York: Alfred A. Knopf, 2005.

MESSER,W. B. et al. Emergence and global spread of a dengue serotype 3, subtype III virus. *Emerging Infectious Diseases*, v.9, n.7, p.800-9, 2003.

MONOT, M. et al. On the origin of leprosy. Science, v.308 (May 13), p.1040-2, 2005.

MONTENEGRO, A. et al. Parasites, Paleoclimate, and the peopling of the Americas. *Current Anthropology*, v.47, n.1, p.193-200, 2006.

OSTROW, R. S. et al. A rhesus monkey model for sexual transmission of a papillomavirus isolated from a squamous cell carcinoma. *Proc. Natl. Acad. Sci.*, v.87, p.8170-4, 1990.

RESZKA, A. A. et al. In vitro transformation and molecular characterization of Colobus monkey venereal papillomavirus DNA. *Virology*, v.181, n.2, p.787-92, 1991.

ROTHSCHILD, B. M. et al. First european exposure to syphilis: The Dominican Republic at the time of Columbian contact. *Clinical Infectious Diseases*, v.31, p.936-41, 2000.

ROTHSCHILD, C.; ROTHSCHILD, B. M. Occurrence and transitions among the Treponematoses in North America. *Chungará* (Arica), v.32, n.2, p.147-55, 2000.

SALEMI, M. et al. Dating the common ancestor of SIVcpz and HIV-1 group M and the origin of HIV-1 subtypes using a new method to uncover clock-like molecular evolution. *The FASEB Journal*, v.15, p.276-8, 2001.

SHARP, P. M. Cell, v.108, p.305-12, 2002.

WANG, E. et al. Evolutionary relationships of endemic/epidemic and sylvatic dengue viruses. *Journal of Virology*, v.74, n.7, p.3227-34, 2000.

WIRTH, T. et al. Deciphering host migrations and origins by means of their microbes. *Molecular Ecology*, v.14, p.3289-306, 2005.

ABSTRACT – Homo sapiens was born with infectious agents that circulated in the common ancestral animal from which both man and the chimpanzee evolved. We acquired other microorganisms while still in African territory, back in the time of the hunter-gatherers. We left Africa, conquered the globe and became sedentary. We discovered agriculture and animal domestication, and this exposed us to more infectious agents. The microorganisms came along with human locomotion. They were present in the human migrations from Africa, in the military campaigns of Antiquity, in the ocean voyages of discovery, during colonization, in the slave trade and so on. The advance in the studies of microorganism DNA and RNA clarifies the origin and spread of various infectious diseases. We can then find out how viruses, bacteria and parasites have globalized since man emerged out of Africa.

KEYWORDS: History, Epidemics, DNA, Globalization.

Stefan Cunha Ujvari is an infectologist at the Hospital Alemão Oswaldo Cruz, São Paulo. He is the author of A história e suas epidemias [History and its epidemics] (Senac, 2003), Meio ambiente & epidemias [The environment and epidemics](Senac 2004) and A historia da humanidade contada pelos virus [The history of humanity told in viruses] (Contexto, 2008). @ - Stefan_cunha@uol.com.br.

Received on 9.22.2008 and accepted on 9.29.2008.

Translated by Anthony Doyle. The original in Portuguese is available at http://www.scielo. br/scielo.php?script=sci_issuetoc&pid=0103-401420080003&lng=pt&nrm=iso.