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Introduction to Cysticercosis and Its Historical Background

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1. Introduction

In this chapter we are going to introduce some relevant aspects on neurocysticercosis (NCC) and its background history in a sequence not previously reported in the medical literature.

Neurocysticercosis is a parasitic infection of central nervous system (CNS) caused by the larval stage (*Cysticercus cellulosae*) of the pig tapeworm *Taenia solium*. This is the most common helminth to produce CNS infection in human beings. The occurrence of acquired epilepsy or the syndrome of raised intracranial pressure in a person living in or visiting a region where teniasis is endemic or even in one living in close contact with people who have taeniasis should suggest a diagnosis of cysticercosis [1-4].

Neurocysticercosis may remain asymptomatic for months to years and sometimes its diagnosis is made incidentally when neuroimaging is performed. Symptoms and signs are related both: the parasite and the inflammatory-immunological response of the host. NCC is the most common cause of acquired epilepsy worldwide and most of the patients taking valproate acid, sodium valproate or carbamazepine for a proper control of their seizures, respond very well [2,5].

Neurocysticercosis is also an important cause of ischemic stroke secondary to infectious vasculitis [4]. The most common cause of epilepsy due to NCC is a calcified lesion with or without evidence of perilesional edema. The prognosis of this situation is worse when there is an associated intraventricular cyst that usually does not respond well to praziquantel and then Albendazole should be prescribed [6].

Parasitic diseases have occurred through the times and they caused more deaths and economic damage to humanity than all the genocidal wars together. Generally in countries with little socioeconomic development is where parasitic diseases occur more frequently, still favored this due to the climatic conditions (warm or temperate) and by the lack of

health education in the population; as in the developed countries social, medical and economic, the parasitic diseases have been eradicated or have very little significance [4,7].

The NCC is a disease closely related to poverty in general, and in particular with a poor personal hygiene and lack of food hygiene, sociocultural and environmental factors, education for health in the community, and also very closely related to the sanitary conditions of each region. This is a preventable disease and able to be eradicated [8], which currently affects more than 50 million people around the world, of which 400 thousand lives in Latin America [9].

According to WHO figures confirmed by Roman and collaborators [10] around 50 thousand people die each year as a result of the NCC and epilepsy secondary to NCC (ESNCC).

The infection by *T. solium* produces two different diseases: taeniasis (TE) and/or cysticercosis (CC). When humans eat eggs of *T. solium* they acquire CC that can be found in any tissue including heart, liver, lungs, and peritoneal cavity [11-16]. The location of the cysticercus (CT) in the CNS and in the retina (considering the retina as an extension of the CNS) is called NCC and is considered the most important neurological disease of parasitic origin in humans and the main cause of late-onset epilepsy [16-18]. Cysts of NCC are located mainly at the distal vascular territory in the cortical gray substance or at the level of the connection between substance gray and white where the blood supply is remarkable including in HIV patients [19].

It is considered that the CC is an important health problem in several developing countries where the social, economic and cultural conditions favor the maintenance of this zoonotic disease and it is seen as a growing community problem in those developed countries with a high rate of immigrants from endemic areas. WHO includes the NCC between neglected diseases or forgotten that cause a significant impact on the economy in several regions from all over the world. It affects 4% of the population in endemic areas [20, 21] where hygiene, habits-food and sometimes religious trends can determine the incidence and prevalence of the disease, for example: The Islam [4].

Islam was not the first religion to prohibit the consumption of pork, before the made Judaism with perhaps less severe restrictions, of all forms no ingestion of pork is not a defense to acquire the NCC, in fact have been reported cases in the Jewish community in New York [22].

Due to globalization, a growing number of uncontrolled immigrants coming from an endemic area of Latin America come to the USA every day, significantly increasing the number of cases of the NCC in the country especially in Texas and California. [11-13, 17,18,22-27]

In total 1494 patients with NCC were confirmed between 1980 and 2004 of which 66% suffered from epilepsy, 16% had an obstructive hydrocephalus and 15% headache due to NCC (91 %), intraventricular (6 %) or subarachnoid (2 %) either because travelled to endemic areas, were of Hispanic origin or had any contact with carriers of the parasite. (Wallin & Kurtzke, 2004; Uddin et al. , 2010)

In Latin America has been described the existence of the NCC in 18 countries with an estimated 350,000 patients infected by the complex CC/TE. In the year 2008, Pawlowski stipulated that in the world would have approximately 2.5 million people infected *T solium* and at least 20 million with CC. In his manuscript, Hotez [9] reported that in the United States were documented between one and two cases of NCC per year, considering that in the growing Latin population could have more than 41,000 Hispanics suffer from NCC [9, 28, 29].

The NCC is also frequent in certain countries in Europe such as Romania, Poland and even Portugal. In Spain the growing vogue of the migration of individuals coming from endemic areas has conditioned an increase in the frequency of this entity [30]. Apart from intraparenchymal NCC (NCCIp), there are some uncommon locations in the NCC that can be divided into: ventricular NCC (NCCiv), subarachnoid NCC (NCCSa), intraspinal NCC (NCCIs), and intraocular NCC (NCCIo) and there many well documented cases reported in the international medical literature [3,4, 31-59]. Some authors report a list of frequencies for these presentations including combinations among them, that we reproduce as follow: NCCIp (55.23 %), NCCiv (15.69 %), NCCSa (11.63 %), NCCIm (3.4 %), NCCIo (0.58 %), and insular neurocysticercosis (NCCI) (0.68 %) and the frequency of demonstrations combined in the following manner: Iv-IP (6.98 %), SA-IP (3.49 %) and SA-Iv (2.32 %) [4, 38].

In a hospital-based study conducted in Mexico, a rate of up to 8.6 cases of NCC for each 100 hospitalized is reported, and in the series of autopsies performed on up to 2 453 per 100 000 inhabitants and it is pointed out that 43.3 % of the cases were asymptomatic [34] and 80% were autopsy findings [60]. Official statistics report an annual average of 500 cases of NCC, with a national rate of raw 0.6 per 100,000 inhabitants [61-63] this report does not include cases uncovered by the health personnel or that were not included in the study for other reasons, it does not include the extra- parenchymal presentations, or other forms of CC as well. In Brazil, the prevalence in autopsies varies from 0.12 to 9%, in the series of clinical cases varies from 0.03 to 7.5 %, and in sero-epidemiological studies from 0.6 to 5.2 %. [64] In Colombia there is not much information on the NCC, only some work in the departments of Antioquia and Santander that reported the 1 and 2% of affectation to the population, and 2% in Ecuador. [65,66] On the other hand, has been estimated that over 50 million people are infected with the complex TE/CC in the world, of which 350 thousand lives in Latin America [67] especially in those countries that do not have an adequate infrastructure and the level of education for an appropriate health. [18, 68] The main risk factors associated with the CC are the presence of TE in members of the community, free-range pigs ingesting contaminated human feces [69] and the use of infested feces as agricultural fertilizer.[70] The NCC has become a public health problem in different countries of Africa, Asia and Latin America. [18, 71-78] Patients presenting NCC in Dominican Republic are located in the southern region and most of then are admitted with epilepsy. [79] In Venezuela the characteristics of the disease are also known and in spite of the fact that there are not many articles published in indexed journals, it was able to obtain some information from summaries of medical congresses [80,81], brochures for teaching purposes [82] and other printed materials [83-85]. In a study conducted in the Teaching Hospital of Maracaibo

(Zulia state), patients diagnosed with CTs or MRI in a period of 10 years, they reported clinical features of 15 patients with NCC. In this study, data obtained were recorded in a protocol sheet with 30 different aspects and analysis of the data is reported with absolute numbers or percentages. The most frequent clinical manifestations were the following: headache (27 %), seizures (20 %), blurred vision (13 %), nausea and vomiting (13 %), dizziness and vertigo (13 %), loss of consciousness (7 %) and in a 7% loss of muscle strength. [86]

Headache (hemicranial or bilateral) is a common symptom to almost all forms of NCC and it is often confused with migraine without aura or tension headaches. This aspect has been disseminated through the popular television program "Dr. House" by what is known by a large audience [87], however in the rest of the studies analyzed the convulsive manifestations were the most frequent clinical manifestation of the NCC and it was observed in 50% to 80% of cases, particularly in patients with lesions in the brain parenchyma for both: children and adults. [4,5 13, 18, 23,24, 34, 61, 67,70,86, 88- 105]

The prevalence of epilepsy has been studied in several African countries. In a rural area of northern Tanzania , 7,399 people were surveyed and found a prevalence for the epilepsy of a 11.2 /1.000 [95% CI 8.9 -13.9/1.000] prevalence for the active epilepsy was: 8.7 /1.000 (95% CI 6.7 -11/1.000) with a predominance of females, the average incidence in the last five years was 81.1 /100,000 (95% CI 65- 101/100,000), 54% (45 of 83) of the respondents were widespread attacks of unknown cause. The 71% (59 of 83) of the epileptic seizures had not been dealt with in an institution of public health and 76% (63 of 83) had never received treatment with DAE [106]. In 2005, de Preux & Druet-Cabanac [107] reported that studies on the incidence and prevalence of epilepsy in the sub-Saharan Africa is very scarce but the prevalence of epilepsy is two or three times higher in tropical countries compared with highly developed countries. Very few cases-control studies have been conducted on the African continent in search of the most common causes of epilepsy but all authors agree that the NCC is without doubt the most frequent cause of epilepsy in the sub-Saharan Africa. [107]

2. Background information

A known scientist said: "The past is the key to the present. Historical studies involving tapeworms contribute to a predictive foundation for understanding today's environments and communities of living things. Besides telling us something about their hosts, parasites can tell us about their geographical links to long ago. They're both the products of a current environment and, at the same time, of a long ancestry reflecting millions of years of association with their hosts." [108].

Homo ergaster is represented by fossils such as "Nariokotome Boy" (Figure 1). They lived during the Lower Pleistocene epoch (dated at between 1.51 and 1.56 million years old), with fossils dated between 1.8 and 1.2 million years old. Some scientists have split *H. erectus* into three separate species, based on the geographic region in which specimens have been found: *H. ergaster* (Africa), *H. erectus* (Asia), and *H. heidelbergensis* (Europe). However, the discovery of *H. ergaster* fossils outside Africa are forcing a reanalysis of this species. *H. ergaster* has

thinner cranial bones, a higher cranial vault, a less robust face and lighter frame than *H. erectus*. [109] For the case made in this listing, all *erectus*-like specimens from Africa will fall under the classification of *Homo ergaster*.



Figure 1. Shows shape of the face and skull of the *H. ergaster* who is the ancestor of later *Homo* populations [109].

The use and control of fire, a milestone in human development, occurred 1 to 1.5 million years ago. Control of fire may have enabled *Homo erectus* to migrate out of Africa. *H. ergaster* fossil finds are not associated with evidence of fire use. Modern humans share the same differences as *H. ergaster* with the Asian *H. erectus*, leading to the possibility that *H. ergaster* is the ancestor of later *Homo* populations. [109]

As a clue to a part of our evolutionary history, scientists have studied the evolutionary relationships of our host-specific taeniid tapeworms: *Taenia saginata*, *T. asiatica* and *T. solium* and those of other species. [108]

This is done by looking at genetic and host differences among tapeworm species. A tapeworm's life cycle is adapted to its parasitic existence. For taeniids, this centers upon a predator-prey relationship, with a carnivore carrying the adult tapeworm and a herbivore hosting the infective larvae. Evolutionary relatives of our tapeworm are usually found in the intestines of carnivores such as lions, hyenas or African wild dogs.

Tapeworms that plague humanity originated in carnivores such as lions and hyenas, and jumped to humans after we began eating their prey animals on the African savannah.

This contradicts the long-held view that humans acquired tapeworms from our domesticated livestock, cattle and swine, following the agricultural revolution around 10,000 years ago.

In a 2001 published paper by Eric Hoberg [108] and his collaborators about the origins of the *Taenia* tapeworms in humans based on genetic analysis of a wide variety of tapeworm species they found that the human-infecting varieties were most closely related to those that

infect modern lions and hyenas. According to Hoberg and his colleagues, tapeworms probably jumped from predators to humans between 2 and 2.5 Mya, when hominids inhabited savannah environments in sub-Saharan Africa and were likely hunting or scavenging the same prey favored by hyenas and lions. Of the three tapeworms that infect people today, the researchers linked one, *T. solium*, closer to a species that uses hyenas and African hunting dogs as its hosts. The other two, *T. saginata* and *T. asiatica*, are linked more closely to a species with lions as its host. Because *T. solium* and the pair *T. saginata*/*T. asiatica* are only distantly related, it appears that two tapeworms independently made the jump to hominids: the ancestor of *T. solium*, and a single parent species of both *T. saginata* and *T. asiatica*. The hyenas in a group are more dangerous than the lions but easier to repel what may have favored a preference for food hunted by hyenas. The amount of genetic difference between *T. saginata* and *T. asiatica* suggests that they split from a single human-adapted species by 160,000 years ago. [108] Worm-carrying human populations may have migrated out of Africa at or before this time, leading to the separation of parasite populations that evolved into the two species. Cattle eventually became the intermediate host in *T. saginata*, pigs in *T. asiatica*.

In 2001, Hoberg [108] said: "Surprisingly, rather than humans' acquiring *Taenia* from cattle and pigs, we believe man gave tapeworms to these domestic animals, because the association between *tuna* and hominids was established before the domestication of these food animals" and second because humans are the most important element in the *T. solium* transmission. Of course, if we take into account that the process of domestication of animal begins some 10 000 years ago and even many of them do not hate in sub-Saharan Africa then it is easy to understand that it was the man who infested cattle and pigs and not in the opposite direction. Probable we owe an apology to the porcine population because we have been blaming something whose responsibility was our ancestors, we think.

Tapeworms are a large group from the so-called 'flatworm' family (known technically as the Platyhelminthes), which are relatively simple creatures with no body cavity, heart, circulatory system or lungs. They are evolutionary simpler than the unrelated but misleadingly similarly named 'roundworms' (also called nematodes), which also parasitize humans and animals. Like most tapeworms, these parasites have a relatively simple life cycle involving a definitive predator host in which the adults live, and an intermediate host in which juveniles reside as tissue cysts called cysticerci. When the predatory definitive host eats (undercooked) meat infected with cysticerci, the cysts hatch and adult worms can grow to meters in size in the definitive host's intestines, producing eggs which pass in the feces and are eaten by the herbivorous intermediate hosts, where upon cysticerci form in the tissues and the life cycle is completed. [108]

Scientists have traditionally adopted an 'anthropophilic' view in which humans acquired *T. saginata* and *T. asiatica* from ancestors of cows, and *T. solium* from ancestors of pigs, following the domestication of these species. But Hoberg's work turns this on its head: one of the closest relatives of *T. saginata* and *T. asiatica* is *T. simbae*. As you might guess from the name, this is a tapeworm whose definitive host is the African lion ('Simba' is Swahili for lion). *T. simbae* cycles between antelope and lions in a typical predator-prey lifecycle.

Similarly, the closest relative of *T. solium* is *T. hyaenae*, which cycles between the predatory hyena and various prey species including Impala and the Sable antelope [108], examination of the evolutionary histories of hosts and parasites and DNA (Shampa, 2009) evidence shows that over 10,000 years ago, ancestors of modern humans in Africa became exposed to tapeworm when they scavenged for food or preyed on the antelopes and bovids, and later passed the infection on to domestic animals such as pigs.

It is assumed that early human ancestors generally had parasites, but until recently there was no evidence to support this claim. Generally, the discovery of parasites in ancient humans relies on the study of feces and other fossilized material. The earliest known parasite in a human was eggs of the lung fluke found in fossilized feces in northern Chile and is estimated to be from around 5900BC. There are also claims of hookworm eggs from around 5000BC in Brazil and large roundworm eggs from around 2330BC in Peru. Tapeworm eggs have also been found present in Egyptian mummies dating from around 2000BC, 1250BC, and 1000BC along with a well preserved and calcified female worm inside of a mummy. [112]

Medical researchers at the Pasteur Institute of Madagascar have travelled around the country, gathering tapeworm from different regions. They isolated DNA from 13 of the samples and then compared their genetic sequences to see how they were related from one to another and to tapeworms from other parts of the world. The family tree of tapeworms they got was strangely ancient and alien. In many cases, the closest relatives of tapeworms on Madagascar are not other tapeworms. The tapeworms that live in the southwest part of the island are closely related to tapeworms hundreds of miles away, in Africa. The tapeworms in other parts of the island are more closely related to tapeworms thousands of miles away, in south Asia.

The scientists then tallied up the mutations in each lineage of tapeworm to figure out how long ago they had split off from a common ancestor. All the *T. solium* tapeworms the scientists studied descend from a common ancestor that lived about 680,000 years ago. The southwest Madagascar tapeworms and the tapeworms of Africa share a common ancestor that lived 235,000 years ago. All of the Madagascar and Asian tapeworms share a common ancestor that lived about 260,000 years ago. The Madagascar tapeworms and their very closest Asian relatives share an ancestor that lived 85,000 years ago. [113]

Pigs and cows were only domesticated within the past 11,000 years or so. The best way to find clues to how these tapeworms colonized us is to compare them to the 39 species of *Taenia* tapeworms that infect wild animals. Eric Hoberg, found that most *Taenia* tapeworms form cysts in wild ungulates, such as antelopes, and then become adults in the carnivores that eat their intermediate hosts. The closest relatives of all three human tapeworms live in Africa. Hyenas are the hosts of the closest relatives of pork tapeworms, while lions are the hosts of the closest relative to the other two species, *T. saginata* and *T. asiatica*. Hoberg and his colleagues compared the mutations in the DNA of *T. saginata* and *T. asiatica* and found that their common ancestor lived somewhere between 780,000 and 1.71 Mya. [108]

The new results from Madagascar fit in nicely with Hoberg's results. Hundreds of thousands of years ago, our ancestors lived in Africa, where they scavenged meat from ungulates. In so doing, it appears, they stepped into the life cycle of *Taenia* tapeworms. Tapeworms that might have ended up in the gut of a hyena or a lion ended up in the gut of our ancestors instead. Over thousands of years, some populations of these tapeworms adapted to our scavenger ancestors. These were the common ancestors of today's human tapeworms, whose great antiquity is now recorded in the DNA of living tapeworms.

The genealogy of the tapeworms also matches up nicely with the human history of Madagascar. People only arrived on the island 2000 years ago. They came from two directions. Bantu farmers sailed from the west of Africa across the Mozambique channel. Asians came from the east, traveling thousands of miles across the Indian Ocean from Indonesia. Malagasy culture emerged from the mingling of these two origins. That culture also includes the livestock that the Bantu and Indonesians brought to the island. And those animals brought parasites with them that had been separated for almost 700,000 years, reaching back to a time when our ancestors had yet to invent fire or spoken language. [113]

In the other hand Hoberg says: "Pathogenic macro parasites, like tapeworms, have parasitized the world's vertebrates and invertebrates for millions of years," "And although they remain a constant threat to economically important fisheries, livestock, and wildlife, only about one-third have been described or named". "Our incomplete knowledge and understanding of taxonomy and species-level relationships of these parasites have hindered our full understanding of their host associations—final and intermediate—and their potential for causing disease." [108]

Southern Africa has provided scientists with a steady flow of Australopithecines, from its numerous caves and quarries. The geological structures here differ quite differently from those in Eastern Africa, in ways that are not as productive to the paleoanthropologist. Although it is not flat by any means, Southern Africa does not have the ground exposure in the form of gorges and ancient river beds, as is the case in the east.

These are phylogenetic studies based on comparative morphology. There is also ongoing research dealing with molecular data, primarily with a research group in Finland. The current hypothesis under examination is that *T. solium* is related to an assemblage of species that circulate in hyenas, and that *T. saginata* + *T. asiatica* (which are sister species) are related to parasites in lions. Both appear to have emerged from Africa. The implication was that the origins of those species now host-specific in humans is related to host switches driven by ecological connections established prior to the origins of modern humans. Current studies suggest that it may be more complicated as the molecular data still support a host switch from carnivores to hominids, but the context may be somewhat different, some papers by Laivikainen, Haukisalmi and their colleagues in Helsinki are exploring *Taenia* phylogeny. (Dr. Hoberg, personal communication on March, 16, 2012)

3. Ancient times

The Biblical Hebrews may have inherited a number of their beliefs from ancient Mesopotamian cultures, among them a conviction that the disease was divine punishment and therefore a mark of sin. This belief was passed on as a basic concept to Christian Medieval Europe. Assyro-Babylonian taboos against close proximity to the sick were also continued by the Hebrews in their isolation of the unclean, who, in addition to the diseased, included the dead, a potential source of soul transference among the Mesopotamian peoples. [114]

The first written records of what are almost certainly parasitic infections come from a period of Egyptian medicine from 3000 to 400 BC, particularly the Ebers papyrus of 1500 BC discovered at Thebes (Bryan, 1930).

In the writings of Greek physicians between 800 to 300 BC, such as the collected works of Hippocrates, known as the *Corpus Hippocraticum*, and from physicians from other civilizations including China (3000 to 300 BC), India (2500 to 200 BC), Rome (700 BC to 400 BC), and the Arab Empire in the latter part of the first millennium, we can find information about parasites as well. As time passed, the descriptions of parasitic infections became more accurate and Arabic physicians, particularly by Rhaze. [112]

Hippocrates was the first physician to systematically classify diseases based on points of similarity and contrast between them. He virtually originated the disciplines of etiology and pathology. By systematically classifying diseases, Hippocrates placed their diagnosis and treatment on a sounder footing. Hippocrates lived a very long life and died at a ripe old age in the town of Larissa in Thessaly. [115]

Hippocrates, Aristotle and Theophrastus called flatworms to worms responsible, either from its resemblance with tapes or ribbons, that Paracelso and Pliny the Elder poured into the Latin and the expression "lubricious latus", worm width. The Arabic medicine, with Serapione also to the head, thought that each proglottid was a worm different. Muslims imposed owning restricted the name "cucurbitineos", not only for its resemblance to the owning miles of the pumpkin, but also because these were one of the oldest remedies against tenacious, still in use. Is attributed to Arnau de Vilanova, at the beginning of the 14th century, the first description of the species. Reflected the old error that only had one parasite per person. [116]

Rhazes was one of the most prolific Muslim doctors and probably second only to Ibn Sina in his accomplishments. He born at Ray, Iran and became a student of Hunayn ibn Ishaq and later a student of Ali ibn Rabban. He wrote over 200 books, including Kitab al-Mansuri, ten volumes on Greek medicine, and al-Hawi, an encyclopedia of medicine in 20 volumes where some advices about the management of parasitic diseases are given [117].

Dioscorides was the first to organize the *material medica* into therapeutic groupings of drugs, based on similarities of medicinal action [118]. We have strong reasons to think that Dioscorides contributed remarkably to the pharmacological treatment of parasitic diseases

in ancient times [118]. If we consider that even the traditional Chinese herbal *materia medica* is organized according to similar therapeutic groupings of herbs, we can see exactly how influential and far-reaching were Dioscorides' revolutionary new ideas.



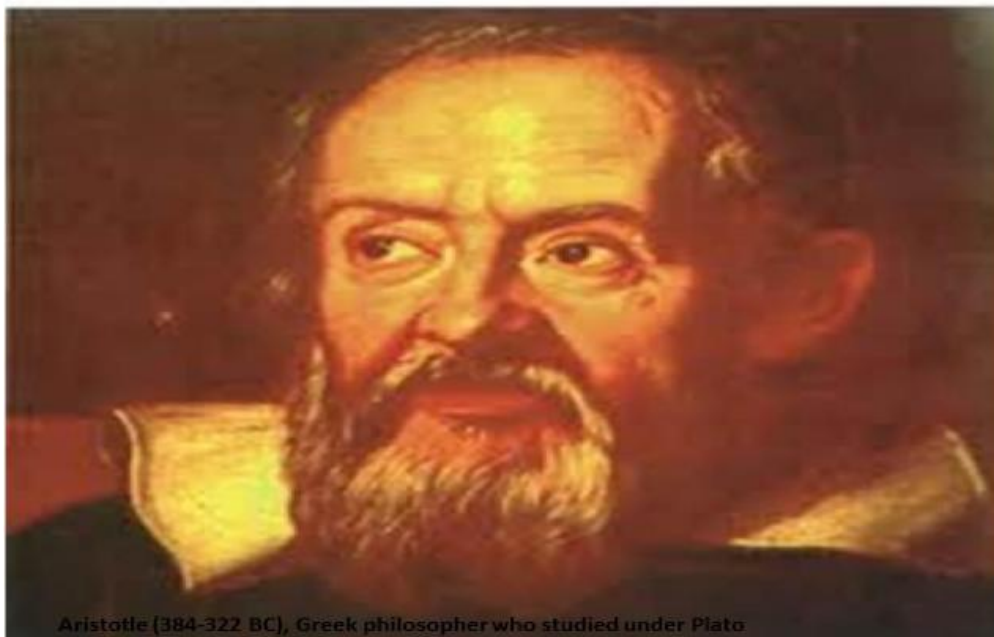
Figure 2. Abu Bakr Muhammad Ibn Zakariya al-Razi (865-925 AD) , known as Rhazes.

Dioscorides' therapeutic groupings by medicinal action have a dynamic, kinetic character: warming, binding, softening, drying, cooling, concocting, relaxing, nourishing and the like.



Figure 3. Pedanius Dioscorides was born around 30 A.D. at Anazarbius (Turkey) in Asia Minor.

The hallmark of infection with the adult worm has been the release of proglottids in the stool. They are also considered symptoms of taeniosis: discomfort abdominal, flatulence, weight loss, and other gastrointestinal disturbances. However, the field research reveals that patients with taeniosis tended to be asymptomatic; not even half the who claim to have past proglottids with bowel movements, however some author reported that the earliest clinical references to tapeworms were found in the works of the ancient Egyptians that date back to *almost 2000 BC*. The background of Cysticercosis as a disease of pigs goes back in ancient times. In the 3th century BC, Aristotle was an epileptic patient probable due to cysticercosis of his brain and in his work "The history of animals", describes the presence of cysticercosis in the tongue and muscles of pigs. Afterwards Plinio (25-79 BC) names the adult form of the parasite *Taenia* (from the Greek *tainia*, which means "lace" or "strip" The background of cysticercosis as a disease of pigs goes back in ancient times.[119]



Aristotle (384–322 BC), Greek philosopher who studied under Plato

Figure 4. Aristotle (384–322 BC), the greatest and most influential of all the Greek philosophers. Aristotle was born at the town of Stageira in the year 384 B.C. His father, Nikomachus, was the friend and physician of Amyntas II, king of Macedonia, father of Philip II and grandfather of Alexander the Great. The description of measles pork in the History of Animals written by Aristotle in the 4th century showed that the infection of pork with tapeworm was known to ancient Greeks at that time [120]. In his treatise "History of animals" Aristotle accurately describes the presence of parasitic larvae in the musculature of the pig: "... The pigs with the soft meat have bladders that are like snowflakes hailing in the region of the thighs, neck and loins; these are the areas that are normally displayed. If there are few, meat is lean; if there are many, meat becomes soft and filled with serous fluid. The pigs that are suffering from this disease are easily recognized, the bladders can be seen on the inner surface of the tongue where they are particularly abundant"; this reference reports clearly pictures of porcine cysticercosis and its main location on the tongue and muscles of the pig. [120]

We could not find enough information to confirm what role Galen played in the management of patients with NCC despite he was the greatest physician of ancient Rome. Whereas Hippocrates laid the foundation of Greek Medicine, Galen further developed its

theory and practice, and carried Greco-Roman medicine to its zenith. Galen became the personal physician to the emperor Marcus Aurelius. [121]

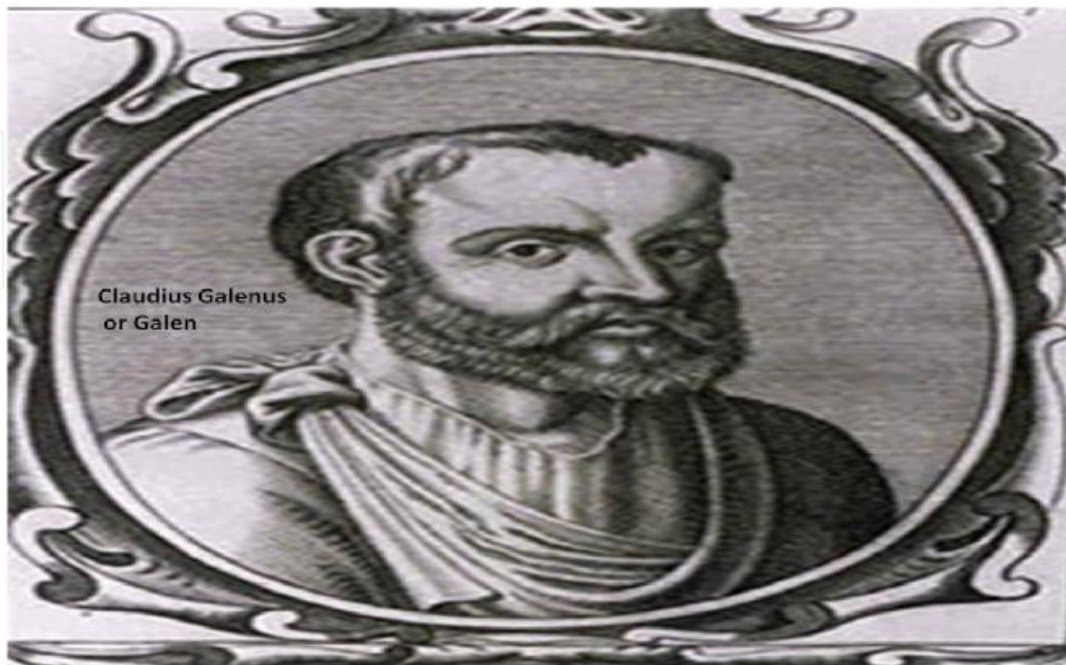


Figure 5. Claudius Galenus, or Galen, was born in Pergamum, an old Greek city on the Aegean coast of Asia Minor, or present day Turkey, in the year 130 A.D.

Theriac was an herbal jam or electuary with some 64 different ingredients that was a virtual panacea or cure-all for many diseases, and an antidote to many poisons made by Galen. Theriac's use and manufacture continued until the late 19th century. Since Venice was a key center for its manufacture, it is sometimes called Theriac Venezian, or Venice Treacle. Today, Theriac Venezian is a key ingredient in Swedish Bitters, an herbal elixir popularized by the Austrian herbalist Maria Treben. [121] We strongly suspect that Theriac was a medication of choice for many patients presenting parasitic diseases including *T. solium* but we found no way to probe it, and unfortunately most of the 80 Galen's treatises are missing.

At this time, there was strong suspicion about contaminated food and parasitic diseases, it was also known to Jewish [114] and later to early Muslim physicians and has been proposed as one of the reasons for pork being forbidden by Jewish and Islamic dietary laws but most probable they had other reasons. Much has been made of a presumably medical basis for the food prohibitions in Jewish tradition, but there may be other explanations. One recent suggestion is that the taboo against pigs was originally related to their competition with humans for water and grain (scarce commodities in a barren land), in contrast to cattle and sheep which consume relatively little water and graze on forage inedible to man.

The rules prohibiting the intake of pork in the religions that have appeared in the Hellenistic period such as the Judaic and later the Muslim possibly related to this and other parasite in muscles. Some of the rules of the Koran are clear indications hygienic aimed at the prevention: "believers brush your arms up to the elbow ... And brush your feet until the

exactly when the NCC was really confirmed for the first time in the history of medicine. As a general agreement it is accepted that NCC is a millennial disease about which there is an early description made Paracelsus and another three centuries later on its relationship with the parasitic infection by *T. solium*. [125, 126]



Figure 7. Paracelsus' reputation as a great doctor preceded him.

The first reference to a case of human cysticercosis we owe it to Johannes Udalric Rumler in 1558, who attributed it to a tumor of the dura mater of an epileptic patient but better description was made by Celsus however, the connection between tapeworms and cysticercosis had not been recognized at that time. [112, 127]

Some authors have raised the NCC helped change the history of the ancient world in the person of Julius César whose epilepsy late-onset (54 years old) greatly influenced their behavior. [128] Domenico Panarolus in 1652 noted similar cysts in the corpus callosum of the brain of another epileptic seizure. But not alludes to its parasitic character up to 1697, when Marcello Malpighi discovered the animal origin of these cysts and described the scolex. [129]

In 1784, Johann August Ephraim Goeze, alien to the work of the Malpighi re-examined in the cysticerci pork and identified its nature helminthic owning. Two years later, P. C. Werner rediscovered the human cysticercosis owning an in the autopsy of a soldier; found two cysts in the pectoral muscle that reminded him they observed in porcine cysticercosis. [129]

In this same period Morgagni determines the similarities between the cysticerci of pork and those found in human musculature. The "hidatogena was described by Fischer in 1789. In 1818 it gives you the name of "cysticerci fisherianus" attributed to Laenec on the basis of "kistis" bladder, "kestus tail, and "fisherianus" in honor of its discoverer. Was Laenec who first introduced the term "cellulosae" [130].

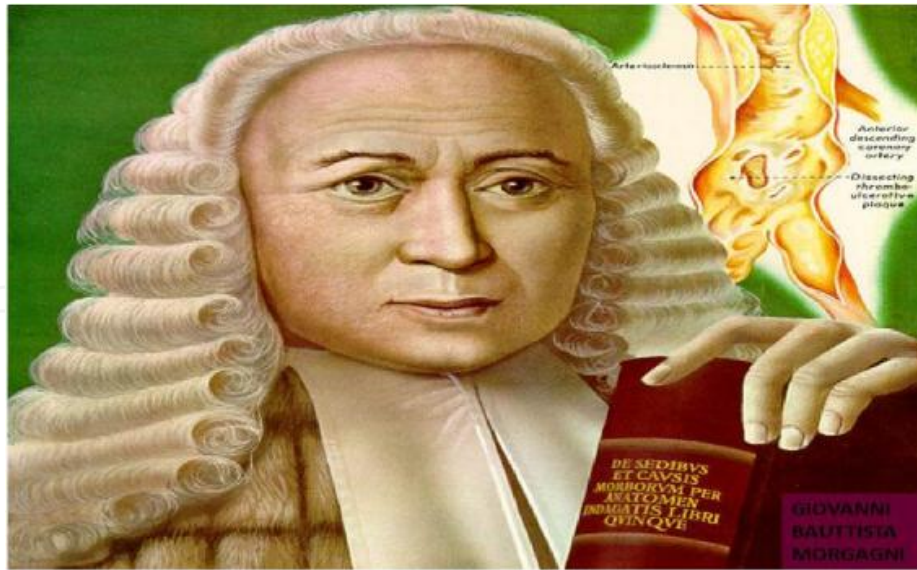


Figure 8. Giovanni Battista Morgagni: Italian anatomist and pathologist, born in February 25, 1682, Forlì; died December 5, 1771, Padua.

In 1829, the first description of the infestation of cysticercus to the anterior chamber of the eye is made [130] being it the first report about active cysticercus in living people. He believed in contagion and would not dissect patients with tuberculosis or smallpox. Virchow considered that Morgagni introduced modern pathology, «with him begins modern medicine» in summary he made discoveries similar to those of Paracelsus [132].

Abraham Gottlob Werner (German geologist) was born in Wehrau, Upper Lusatia, now Polish Osiecznica, on 25 September 1749. In 1786, Werner determines the similarities between the cysticerci of pork and those found in human musculature. That controversy was the focus of much geological activity through the end of the 18th century, and well into the 19th century and although at the end of the 18th century taeniosis and cysticercosis were well known by him because the biological cycle of the parasite is ignored, the association between them was not identified among the greatest scientific at that time [133]. Goes in 1784 and Felix Dujardin in 1845 noted similarities in the shape of the scolex of the adult worms with the cysticerci and suspected a relationship between the two [129].

A first step was taken in the discovered owning of the eggs of flatworms. Some were raised then the formation of the adult worm. The "taenia hidatigena" was brought by Fischer in 1789. René-Théophile-Hyacinthe Laennec invented the stethoscope in 1816, while working at the Hôpital Necker and pioneered its use in diagnosing various chest conditions [134].

Laennec was a gifted student, he learned English and German, and began his medical studies under his uncle's direction. Laennec studied medicine in Paris under several famous physicians, including

Dupuytren and Nicolas Corvisart des Marest [130]. He was trained to use sound as a diagnostic aid. Corvisart advocated the re-introduction of percussion during the French Revolution. Laennec was a devout Catholic. He was noted as a very kind man and his

charity to the poor became proverbial [134]. In 1818 the name "cysticerci fisherianus" was given by Laenec based on "kistis" bladder, "kestus queue, and "fisherianus" in honor of its discoverer. Was Laenec who first introduced the term "cellulosae" [131].



Figure 9. Laennec (17 February 1781 – 13 August 1826) was a French physician.

The first description of the infestation of cysticercus to the anterior chamber of the eye is made in 1829 [130].

The development of cysticerci in pigs has been demonstrated in 1853 when Pierre Joseph Van beneden fed to a pig with *T. solium* eggs and found cysticerci in the muscles during necropsy. Van beneden used as animal control to another pig that was kept in the same conditions, but without giving eggs; in this found no cysticerci. At this time Van Manedem sets out the "law of the transmigration of the tapeworms" [130].

Two years later, in a controversial study, Friedrich Kuchen showed that tapeworms are developed from cysticerci.

Around 1850, Kuchenmeister fed pig meat containing cysticerci of *T. solium* to humans awaiting execution in a prison, and after they had been executed, he recovered the developing and adult tapeworms in their intestines. By the middle of the 19th century, it was established that cysticercosis was caused by the ingestion of the eggs of *T. solium* (Shampa, 2009)

In December 1854, Aloys Humbert is auto infected eating 13 cysticerci; toward March of the following year began to expel segments of *T. solium* [129].

The first pathological descriptions and their respective clinical correlations were made by Virchow in 1860, who also identified the location basal meningeal of this parasite calling cysticerci multilocularis" [130].

Leuckart earned his degree from the University of Göttingen, where he was a student of Rudolf Wagner (1805-1864). Leuckart is remembered for his work in Parasitology,

particularly research regarding tapeworm and trichinosis. He was the first to prove that *Taenia saginata* occurs only in cattle (and humans), and *Taenia solium* occurs only in swine (and humans). His study of *Trichina* helped support Rudolf Virchow's campaign to create meat inspection laws in Germany. With Virchow and von Zenker, he was the first to document the life cycle of the parasite *Trichinella spiralis* in swine and humans.

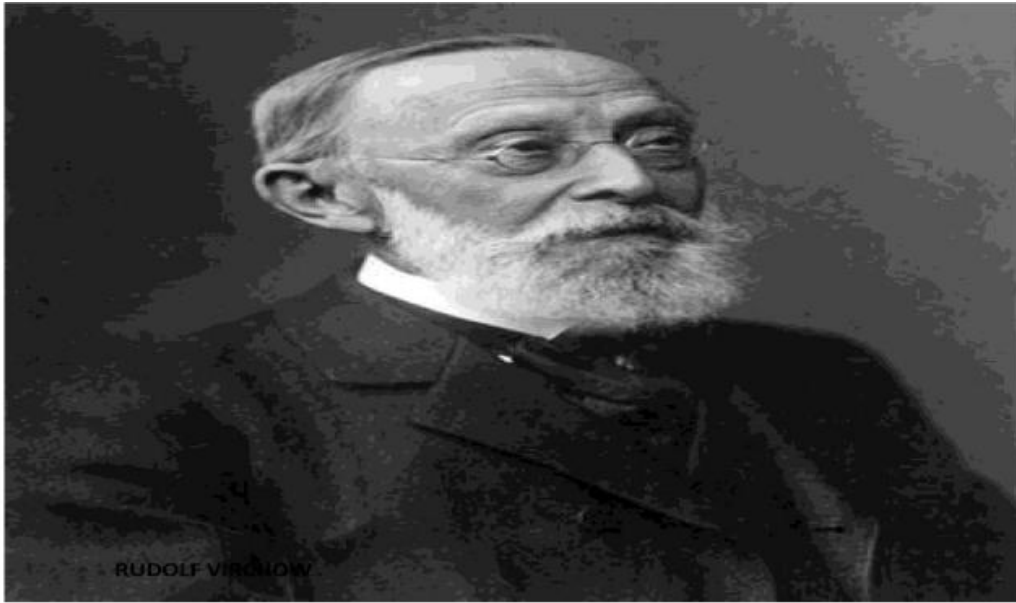


Figure 10. Rudolf Carl Virchow (13 October 1821 – 5 September 1902) was a German doctor who made many great discoveries.

He also made important studies of the sheep liver fluke. Leuckart is credited with splitting George Cuvier's Radiate into two phyla; Coelenterata and Echinodermata. Today the "Rudolf-LeuckartMedaille" is an annual award given for research in Parasitology by the Deutschen Gesellschaft für Parasitologie (German Society of Parasitology). [138]

Zenker was born in Dresden, and was educated in Leipzig and Heidelberg. His important discovery of the danger of trichinae dates from 1860 he made studies on *T solium* but his results are not well documented. In that season he published "Ueber die Trichinenkrankheit des Menschen" (in volume xviii of Virchow's *Archiv*. [139]

Also in 1862, Griesinger analyzes a series of 86 patients, and it establishes a direct relationship between cerebral cysticercosis and epilepsy, and proposes a first classification of disease. The term "cysticerci multilocularis by cysticercus racemose" was permanently changed by Zenker in 1882 [130] and three years later Kuchenmeister discovers that the cysticercus is the larval stage of *Taenia solium*. [131] Askanazy discovers the arterial lesions: "temporal arteritis obliterant disease" and it was attributed to cysticercosis in 1890. [140]

In the 19th century some people attributed the pig taboo in the Middle East to the danger of the parasite trichina. Marvin Harris posited that pigs are not suited to being kept in the Middle East on an ecological and social-economic level; for example, pigs are not suited to

living in arid climates and thus require far more water than other animals to keep them cool, and instead of grazing they compete with humans for foods such as grains. As such, raising pigs was seen as a wasteful and decadent practice. A common explanation to the fact that pigs have widely been considered unclean in the Middle East is that they are omnivorous, not discerning between meat or vegetation in their natural dietary habits. The willingness to consume meat sets them apart from most other domesticated animals which are commonly eaten (cattle, horses, goats, etc.) who would naturally eat only plants [139]. At the end of the XIX century cysticercosis was already spread on all over the Europe until 1900 when Germany began an effective fight against CC/TE creating a law for the obligatory inspection of the porcine population confirming a decrease in the frequency of cysticercosis of the 2% to 0.1 %. [130]

In Ecuador the first descriptions were carried out by the Dr. Valenzuela (1901) who reported the first case of NCC in Guayaquil [141]. Doctor Valenzuela from Ecuador made the first descriptions on CC in 1901 and reported the first case of NCC in Guayaquil [141]. In 1906, Hennenberg performs a comprehensive review of the topic and modifies the first classification proposed by Grisinger and Hennenberg. [130] Between 1909 and 1911, Moses and Wimberg began serologic studies for diagnostic purposes using complement fixation in serum. [131]

In 1932, Heinert describes 11 patients diagnosed with *T solium* in Ecuador [130]. Salazar-Viniegra describes in Mexico for the first time (1936) the CC of the CNS in deceased from the bedlam of the Mexico City [142]. Spider and Asenjo by means of the gaseous ventriculography diagnosed a case with NCC in the posterior fossa (1945) and one year later in Chile Coastal publishes its findings in the General Hospital of Social Security in Mexico, finding evidence of CC in the 3.6 % of autopsy material. In this same year Robles published 47 cases treated surgically. In Argentina, Dickmann was the first to communicate their results on NCC in the child population from that same year. [143]

In 1948 Nieto [144], reported that 11% of the Mexican patients admitted to the neurology service of a general hospital, and 0.8 % of the interneers in a psychiatric hospital presented NCC, while Stepien and Choroboski a year after reporting a series of patients treated surgically with success, an opinion not shared by the great neurosurgeons of the era; on that date Arseni reported 65 patients with NCC verified in a period of 20 years (1935-1955) by highlighting that it was hereditary or affecting other countries. Returning to Latin America, it is reported that in Mexico the 3.6 % of the hospital autopsy showed evidence of CC. [140] In the year 1965 in Ecuador the first findings of autopsies are attributed to Guerrero. In Brazil, the prevalence of NCC increased up to 2.9 % in that same year and in 1970 the prevalence of the NCC in the hospitals of neurosurgery and neurology in Colombia was 0.9 %. [130] Mora-Rubio (1971) in Colombia reported 114 confirmed cases of NCC. In 1972 there was a cooperative study in Latin American countries, remain at the forefront of this research Sixto Obrador who found a decrease in the CC with tumor presentations "intracranial lesions expansionary" of 3% in 1950 to 0.6 % in 1960 [145] his work is considered a classic monograph on this topic. [146] The first reports on the treatment of the CC on the American

continent were reported in 1983 (Andrews & Thomas) followed by the publication of a guide for the management, prevention and control of the complex CC/TEA prepared by the WHO. In 1985 was a collaborative study of the NCC in the hospitals of the city of Los Angeles that grouped 497 patients (Richards et al. ,) while Sotelo (1985) in Mexico publishes a new classification for the NCC based on the presence of active and inactive forms. In 1987-1989, Sotelo proposes a plan for management of NCC according to the characteristics and tomographic studies of CSF. An episode recorded in 1934 enabled us to establish the time of appearance of the symptoms of the disease. In that year, British soldiers stationed in India returned to their country and some of these soldiers were diagnosed as NCC, for which they were subjected to a strict medical follow-up. Seizures, as the main symptom, took on average two years to appear, although there were cases where the epilepsy has lasted up to 20 or more years since their return. [129]

Over 1973, as a result of the increase in technology and the onset of the CT scan that it would be in the long run the fundamental pillar of the diagnosis and treatment of the cysticercosis increases the number of publications with respect to the topic and in Mexico, the frequency of the NCC in the specialized hospitals was 4%. [130]

The frequency of the NCC in the hospitals of Neurology and Neurosurgery in México (1973) increased up to 10 %; while in the general hospitals of Ecuador it was 2.6%. [130]



Figure 11. First International Congress on Cysticercosis, San Miguel Allende, Mexico, November 1981 (Source: Cysticercosis Present State of Knowledge and Perspective. Edited by Ana Flisser, Kaethe Willms, Juan Pedro Laclette, Carlos Larralde, Cecilia Ridaura; Fernando Beltran. Red Book, was published in 1982. (Courtesy of Dr. Flisser)

The First International Meeting on Cysticercosis was held in Mexico in 1981 with a good participation of international scientists. (Figure 16)

In 1982, Zenteno publishes a classification of human cysticercosis and in 1983 appear the first reports of treatment of the cysticercosis. The World Health Organization published a guide for the management, prevention and control of the complex taeniasis/cysticercosis (WHO, 1983). One year later The World Health Organization, indicates that the world's population already was 5,000 million inhabitants and that the taeniasis were 1.5 % [130].

1985 Was conducted a collaborative study of the NCC in the hospitals in the city of Los Angeles that grouped 497 patients (Richards, 1985). Sotelo in Mexico publishes a new classification of NCC based on the presence of active forms and inactive (Sotelo, 1985) and two years later he proposes a management scheme about NCC with categorization tomographic and studies of cerebro-spinal fluid. [146]



Figure 12. Upper left, Cestodes Symposium held in Australia, 1986 . Upper right, Neurocysticercosis Symposium in Mexico. Lower left: Cysticercosis meeting in France, 1994. Lower left: Cysticercosis meeting in Perú, 1993 (Courtesy of Dr. Flisser)

In 1988, Italy has been carrying out a review of all published cases of NCC since the beginning of the century and 11 cases were reported, most of them in Sicily. [130] Figueredo de Coimbra warned of an increase in the incidence of NCC in Portugal by the presence of population from African colonies. [130] Stanol and collaborators propose a new prognostic classification of NCC (Español, 1986). Madrazo and Sandoval published a new classification of neurocysticercosis in 1989. [146] In the 1980s there was much emphasis on the immunological diagnosis of the NCC existed a large number of publications highlighting mainly studies on the enzyme linked immunosorbent assays [147-155] and immunoelectron

transfer (EITB) by Tsang and collaborators [156-159] and Wilson [160] plus other contributions made by Flisser a little bit later. [161,162]

In 1990, Medina et al. studied 100 consecutive Mexican patients with epilepsy that started after the age of 25 years. All patients underwent clinical evaluation, computed tomography, and electroencephalography; additionally, cerebro-spinal fluid analysis was performed in 82 of them.



Figure 13. Shows some of most relevant scientists in the field of cysticercosis who attended to the meeting in Atlanta, Georgia on February 24, 2008. From left to right: Phillip S Craig, Akira Ito, Ana Flisser, Peter Schantz and Lee Willingham III (Courtesy of Dr Flisser).

The volume of research and publications on cysticercosis, taeniosis and NCC increased gradually in this decade reaching a large number therefore it is not possible sum it up in the limited space we have but we should not conclude this historical review without prior highlight the meritorious work performed by some prominent researchers in this stage such as: Ana Flisser, Peter Schantz, Julio Sotelo, Hugo García, Oscar del Bruto, Akira Ito, Jefferson Proaño, Vedantam Rajshekhar, Ravindra Kumar Garg, Ted Nash, Carlton Evans, Osvaldo Takayanagui, Clinton White, Lee Willingham, Phillip S Craig, Gagandeep Singh, Sudesh Prabhakar, Hélène Carabine, Andrea Wrinkle, Arturo Carpio, Agnes Fleury, David Botero, Svetlana Agapejev, Gustavo Román, P Dorny, M Raghava, V Prabhakaran, Victor Tsang, Jorge Morales-Montor, Tetsuya Yanagida, Marshall Lightowlers, Elsa Sarti, Joachim Blocher, Yasuhito Sako, Minoru Nakao, Feng Zheng, Kazuhiro Nakaya, Jim Allan, Dolores Correa, Armando Gonzalez, Robert Gilman, García E, Márquez C, Fragoso G, Sciutto E, Cuetter A, Andrews R. Ferrer E., Cabrera Z., T Kelesidis, Tony Velasco, Cortés M, Alain Dessein, Pierre-Marie Preux PM, Jose A Serpa, Linda S Yancey, Pratibhasinghi Singhi, Dumas M, Carlos Larralde, Tapia G, Eon Keeseon, Carlos Larralde, Tammi Krecek, M Gupta, P Agarwal, GA Khwaja, P Sharma, R Shukla, D Singh, MV Padma, NK Misra, GK Ahuja, IK Phiri, Helena Ngowi, Sam Mukaratirwa, LM Michael, S Siziya, Humberto Foyaca, Emilia Noormahomed, Aline S de Aluja, Molina Alvarez, J Lasso, F Quet, M Guerchet, EB

Ngoungou, A Nicoletti, N Wadia, Jorge Burneo, Tonicarlo Velasco, Theodoros Kelesidis, P Huc, M Druet-Cabanac, M Strobel, Li T, Phil Craig, X Chen, D Qiu, J Qiu, MO Sato, T Wandra, H Bradshaw, L Li, N Nakao, J Waikagul, D Wattanakulanich, W Maipanich, K Nakaya, MO Sato, Y Sako, M Okamoto, K Swastika, C I Dewiyani, T Yanagida, K Nakaya, Hiroshi Yamasaki, James C. Allan, Marcello Otake Sato, Minoru Nakao, Yasuhito Sako, Kazuhiro Nakaya, Dongchuan Qiu, S Desai, A Cuetter, AE Gonzalez, S. Geerts, NC Kyvsgaard, DP McManus, ZS Pawlowski. However over this relationship there are still a significant number of researchers that do not appear in the listing.

Most of these scientists have been grouped to work together on the same objective: *Taenia solium*. Some have more than 20 years of experience and more than 20 publications. Among the groups with better results are the groups in México, Perú, and the three groups from Ecuador (Quito, Cuenca, and Guayaquil). There are other groups from the Eastern and Southern Africa (CWGESA), Asia and Oceania, and the group of Europe of recent constitution (Willingham LA III et al., 2008).

The CWGESA was established in 2002 to promote communication, collaboration and coordination of integrated research and control activities to combat cysticercosis, a serious and sometimes fatal disease transmitted between pigs and people by the zoonotic tapeworm, *Taenia solium*.



Figure 14. Cysticercosis Working Group for Eastern and Southern Africa International Training Workshop organized by CWGESA and held on June 2004 Mthatha where delegates from 11 African countries participated.

The 7th General Assembly on cysticercosis/taeniosis was held at the Faculty of Health Sciences, Walter Sisulu University, Mthatha, South Africa, from 20 – 22 July 2011. The meeting was organized by the Cysticercosis Working Group in Eastern and Southern Africa (CWGESA) in collaboration with the Faculty of Health Sciences of Walter Sisulu University. Veterinary, medical, agricultural and socioeconomic researchers met in Mthatha to discuss the Roadmap for Elimination of *Taenia solium* cysticercosis/taeniosis (TSCT) in Eastern and Southern Africa and to evaluate progress and make recommendations on intervention research for the elimination of the disease.



Figure 15. Members of the CWGESA attended to this meeting. Seated from left to right: Lee Willingham III, Samson Mukaratirwa, Humberto Foyaca, Helena Ngowi and Faustin Lekule.

We have the advantage that the disease has been virtually isolated in the communities around Mthatha where there are also human and material resources needed to eradicate the cysticercosis if we receive the necessary support of governmental institutions and non-governmental organizations committed to this goal. Eradicating the cysticercosis of the surrounding area of Mthatha is equivalent to delete the *T. solium* in South Africa and this could be the first country in the world to achieve it.

Mexico is the country that more progress has been achieved in this regard and their doctors and researchers take pride that flag.

4. Honor to honor deserves

For prevention and eradication of cysticercosis are needed peoples dedicated and committed to this cause, which should be headed only by honorable scientists stripped of any trait of hubris, arrogance and self-sufficiency.

In our opinion, the person who has been most prominent in the research work related to the tapeworm *Taenia solium* is the Dr. Ana Flisser as shown below; she is a full time, upper rank, senior scientist at the National Autonomous University of Mexico, UNAM since 1972.

The authors of this chapter believe that in order to be considered a researcher whose example should be followed by the younger generations are they must comply with certain requirements among which protrude the modesty, honesty, solidarity and a desire to help the younger generations of researchers to its best development unconditionally. In our opinion that example is Dr. Ana Flisser.

5. Recent awards and distinctions received:

Dr. Ana Flisser won the University Award 2011 in Research in Natural Sciences.

Coordinator of the first MD/PhD Program in Mexico, UNAM, 2011.

First Vice-President of the World Federation of Parasitologists and President of the XIII International Congress of Parasitology to be held in Mexico City in August 2014

Award Ciudad Capital “Heberto Castillo Martínez” Research in Health and Environment, 2008 President, From Alaska to Chiapas: The First North American Parasitology Congress, Merida, Yucatan, June 21-25, 2007

Director of Research, Hospital General “Dr. Manuel Gea Gonzalez” SSA, 2001-2005.



Figure 16. Dr. Ana Flisser Department of Microbiology and Parasitology, Faculty of Medicine, National Autonomous University of Mexico.

PAHO Award for Administration 1999. For her work to transform the network of public health laboratories in her country to support priority health programs, including administration, teaching, and research. Director, National Institute for Epidemiology Diagnosis and Reference (INDRE), SSA, 1995-2000.

Research area

Cysticercosis and taeniosis due to *Taenia solium*

Publications

128 original articles in international and Mexican refereed journals. 60 reviews or invited articles

62 book chapters (two chapters in this book are not included). 8 books as editor or coeditor. 3 books as author or coauthor

Advisor of thesis

11 for doctor in science, 12 for master in science, 12 as member of advisory committee, 2 for medical specialties, 15 at the bachelor level

Financial support

20 research projects from: DGAPA/UNAM, CONACYT, European Community, IDRC/Ottawa, WHO/PAHO, Merck-Darmstadt/Merck-México.

Recent teaching activities

Immunoparasitology since 2004, Faculty of Sciences, UNAM. Immunoparasitology in graduate programs since 2005, Faculty of Medicine, UNAM.

Academic activities

483 papers in national and international congresses. 182 national and international invited lectures 44 graduate and bachelor courses. 52 lectures at different graduate courses and various memberships of Societies of Parasitology, Tropical Medicine and Immunology of Mexico, USA and Great Britain, as well as of the International Federations in these areas. (Source: World Federation of Parasitology). Again, we want to emphasize that not only fatten the results to the person, other qualities such as modesty, friendship, solidarity, honesty, and the desire to selflessly help young researchers are also qualities that make an example to follow that I wish to report to the new generations of scientists worldwide.

We would like to make it very clear that we have received from Dr. Flisser some photos to illustrate this chapter but that the decision to include this modest but deserved tribute to her maintained and hard work, is ours. Therefore she had no role in chapter design, information collection, decision to publish, or preparation of the manuscript. By her modesty, we know that she will not fully agree with this decision but we could not ignore her history. To pay a tribute to their achievements including her personal contribution to the reduction of the morbidity and mortality of the cysticercosis in Mexico and everything she has done by and for the rest of humanity, is right.



Figure 17. Dr. Ana Flisser: Always surrounded by talented young people who receive her teachings, experience and wisdom.

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