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INVITED PAPER

History of Echinostomes (Trematoda)

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Abstract

Echinostomatidae (Trematoda) is the largest family within the class Trematoda. Members of this family have been studied for many years in relation to their utility as basic research models in biodiversity and systematics and also as experimental models in parasitology since they offer many advantages. Echinostomes have contributed significantly to numerous developments in many areas studied by parasitologists and experimental biologists. In this review, we examine the history of the echinostome-based studies from the beginnings to the present. For this purpose, we have divided the history of echinostomes into four periods (i.e. 18th and 19th centuries, first half of the 20th century, second half of the 20th century and the late 20th and 21st century) according to the types of studies performed in each of them. Moreover, we also briefly review the history of echinostome infections in humans.

Keywords

Parasitology, History, Trematoda, Echinostomatidae, *Echinostoma*

Introduction

Echinostomatidae (Trematoda) Looss, 1899 is the largest family within the class Trematoda. Members of this family are parasitic intestinal trematodes that can infect a wide range of vertebrates, including humans, in their adult stage. These adult worms are characterized by the presence of a circumoral head collar with one or two crowns of spines. Their complex life cycle involves three categories of hosts – final, first and second intermediate hosts in which seven different stages (adults, eggs, miracidia, sporocysts, rediae, cercariae, and metacercariae develop). Echinostomes have been studied for many years in relation to their role as basic research models in biodiversity and the systematics of helminths, particularly since the systematics of echinostomes are problematic because of interspecific homogeneity of characteristics to distinguish species. Apart from these aspects, echinostomes have been used extensively as experimental models in parasitology since they offer many advantages such as easy maintenance of their life cycles in the laboratory or their wide geographical distribution. This has determined that echinostomes have contributed significantly to numerous developments in many areas studied by parasitologists and experimental biologists.

In the present paper, we revise the history of the echinostome-based studies from their beginnings to the present. We also give an overview of the evolution of the research on echinostomes that, interestingly, has many parallels with the evolution of general parasitology.

Periods in the history of echinostomes

According to Kanev (1985) there is reason to believe that the first data for obtaining echinostomes in birds dated from the time of Aristotle (384–322 BC). The same author reported on the existing descriptions of parasites by Redi in 1684 but they were not probably the subject of scientific interest until the 18th century. Since then a large number of scientists have worked with these trematodes.

To facilitate the reading and the comprehension of our review, we have divided the history of echinostomes into four periods (i.e. 18th and 19th centuries, first half of the 20th century, second half of 20th century and late 20th and 21st century).

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We are aware that this division can be is rather artificial and somewhat confusing. For example there are several authors that started to work on echinostomes in one of the periods but continued working on them in the subsequent period. However, we hope that our approach will serve to give a good overview of the history of the echinostome-based studies.

18th and 19th centuries

The first historic period of the studies of echinostomes comprises the 18th and 19th centuries. The studies in these centuries consist mainly of faunistic records and the subsequent descriptions of the adults and/or larval stages recorded. This resulted in a large amount of scattered data that made necessary several reviews to collect and systematize all these data.

The studies of echinostomes during the 18th and 19th centuries were mainly intense in Europe and, particularly, in Germany. In that country many findings were made in nature that were followed by the subsequent systematic studies. The number and the quality of these studies have made it possible to speak of a German school. The development of this "school" goes through several stages. In the first stage, between the years 1782 and 1790, have been conducted systematic research after which became available the first clear evidence of the presence of echinostomes. For instance, Müller (1773) described and illustrated as *Cercaria lemna* the first echinostome cercaria. Between the years 1776 and 1790, Schrank described and illustrated as *Fasciola melis*, *Festucaria anatis*, and *Festucaria boshadis*. The first description of larval stages of echinostomes was done by Bermann (1774) who described echinostome cercariae as "*Cercous infusories*". As a result of these findings, Gmelin (1790) revised listings in Linnaeus' Systema Helminthum with the new knowledge about the echinostomes. The next data concerning adults of echinostomes were reported by Froelich between the years 1789 and 1802, when he obtained parasites from birds in Germany and described them as *Fasciola appendiculata*, *Fasciola crenata* and *Fasciola revoluta*. Of particular interest is the description of *F. revoluta* (Froelich, 1802) since it served as the main basis for further definitions of what is known today as *Echinostoma revolutum* that was subsequently selected as the type species for the so-called group *Echinis* (*Echinostoma*) by Rudolphi (1809).

The next stage of the German school development included the period between the years 1800 and 1824. In this phase, Zeder between 1800 and 1809 established a new name for an echinostome, *Distomum echinatum*, and published detailed descriptions of the collar-spines of these parasites (Zeder, 1800, 1803). Collecting the data obtained in a period of ten years (1809–1819) Rudolphi (1809) erected the genus *Echinostoma* and published two new systems: one in *Entozoorum sive vermium* and the second in *Entozoorum synopsis*, establishing *Fasciola revoluta* as a type species. Meanwhile, Bojanus (1818) described and illustrated as "Köningsgelber würmer" the first echinostome redia found in naturally infected freshwater snails. Several years later, Bremser (1924) published *Icones helminthum* with illustrations of *Distoma echinatum* and other adult worms described in Rudoiphi's *Entozoorum synopsis*.

The third stage of the German school development corresponds to the period 1837–1842. Siebold (1837) described for the first time the life cycle pattern of *Echinostoma* and Trematoda in general. This was possible due to his studies using an echinostome cercaria named in the original study as *Cercaria echinata* and eggs, miracidia and sporocysts of *Cyclocoelum* sp., named in the original as *Monostoma mutabile*. This study also included comparative examinations with the illustrations by Bojanus of echinostome rediae from naturally infected freshwater snails.

The final stage of the German school development during the 18th and 19th centuries is connected with the ten year period (1850–1860) when Diesing, using materials from Vienna and Berlin, performed a complete revision of echinostome systematics using data from Zeder, Rudolphi and Bremser that was used in the field of parasitology for many years. Pagenstecher (1857) described *Cercaria magna*, *Distoma echinatoides anodontae* and *D. echiniferum paludinae* from Germany, Wedl (1857) reported, described and figured species which he identified as *D. echinatum* and Cobbold (1860) completed a revision of adult echinostomes and their hosts. Thereafter, v. Linstow described several new species between the years 1873 and 1884 in the group of echinostomes – *Distoma beleocephalum*, *D. recurvatum* and *D. pungens* (see Linstow, 1904) and Looss (1899) erected the superfamily Echinostomatoidea.

In parallel to the above mentioned studies in Germany, several studies were conducted during the 18 and 19th centuries in other countries in Europe and the USA. For example, Abilgaard, in the period 1797–1819 (see in Rudolphi, 1819), and later Steenstrup described several adult and larval stages of echinostomes in Denmark (see Kanev *et al*., 2000). In Italy, Filippi (1854) described an echinostome cercaria released from viviparid snails that was named as *Cercaria echinatoides*. Ercolani (1881, 1882) described several echinostomes such *Cercaria spinifera* in the same country and reported several experiments with this species. Generali (1881) detected adult echinostomes in dogs. Parona (1896) and Stossich (1892) reviewed the echinostome adult worms detected in Italy. Belingham described several echinostomes found in Ireland and Swammerdam (1887/8) described those from the Netherlands. Similarly, Kowalewski (1898) reviewed the adult echinostomes found in Poland. Railliet (1895) described and illustrated adult and larval echinostomes from Europe. In this period, the first echinostome cercaria (*Cercaria agilis*) in Africa was described by Sonsino (1892) and, in the period 1896–1899, Looss described other echinostome adults from Africa (see Looss, 1899). In the USA, several authors detected echinostomes in naturally infected birds and mammals that were named D. *echinatum* following Zeder (1803) (Leidy, 1888, 1904; Stiles and Hassall, 1908; Hasall, 1896).

First half of the 20th century

As occurred in the previous period, the main body of work performed in the first half of the past century was focused on the systematics of the echinostomes. However, there are two main differences with respect to the studies in the previous centuries. Firstly, the studies in the 20th century spread worldwide. Secondarily, the large amount of data collected during the previous centuries made necessary the reorganization of the known data and, thus, several larger revisions were done during this period that have been followed for years by several researchers.

Initially, the studies were still focused in Germany. During the early 20th century, special mention should be made to the work by Dietz (1909, 1910) and Lühe (1909). Dietz (1909, 1910) revised in detail the systematics of echinostomes arranging the group in a total of 22 genera. The work by Dietz served for years as the main basis for the classification of the echinostomatids. Lühe (1909) revised in detail the morphology of several echinostomes. Mendheim after his studies between 1940 and 1943 added knowledge about the parasites of this group in a new taxonomic system for the family Echinostomatidae with 9 subfamilies and 27 genera (Mendheim, 1943). Moreover, several German researchers such as Looss, Braun, Lutz and Dollfus studied the echinostome fauna in other countries and continents. In the rest of Europe, the research continued with many studies such as those by Ratz (1908), who described *Distoma saginatum*, *Pegosomum asperum*, *P. saginatum*, *P. spiniferum* and *E. perfoliatum* adults from birds in Hungary after almost ten years of investigations (1900–1908). Later, Ciurea (1915) studied the biology and hosts of adults and larval parasites from birds, mammals and humans in Romania. Wessenberg-Lund (1934) described in detail the echinostome cercariae found in Denmark. Similarly, Vevers (1923), Brown (1926) and Harper (1929) in the UK and Dubois (1928) in Switzerland studied the larval stages of echinostomes.

An extensive body of work was done in Russia during the first half of the 20th century. The investigations on echinostomes carried out by Russian parasitologists can be divided in several ways: studies on the adult and larval morphology, studies on the species composition and prevalence of echinostomes, studies on the life history and determination of their intermediate and final hosts in Russia. The first record on echinostomes in this school is by Soloviev in 1912 who described *Echinostoma echinatum* and *E. mesotestius* in Turkestan (member of the former USSR). Important contributions to the knowledge for echinostomes are the investigations by Skrjabin and co-workers carried out in Russia during the period between 1913 and 1956 in which have described illustrated and revised descriptions of adults, larvae and hosts of echinostomes. As a result of this work, two revisions and systems were published by Bashkirova in the edited by Skrjabin (1947) "Essentials of trematodology – Trematodes of animals and man" vol. 1 and by Skrjabin and Bashkirova in the vol. 12 of the later review by Skrjabin (1956). The family Echinostomatidae is presented with eleven subfamilies and fifty genera. Apart from the above mentioned authors, interesting studies on echinostomes in Russia were done by numerous authors including Petrov and Semenova, later Dubinina between the years 1937 and 1966, part of which is focused in the morphology, biology and hosts of adults on birds from the Volga River. Other scientists of this school has been worked with adult echinostomes and their larval stages in different places of the former USSR, as Kurova between 1926 and 1927 in Turkestan, Isaichikov, Panova and Ivanitcki during the same period in Ukraine, continued later by Shevtzov and Chernogorenko-Bidulina, studies by Kasimov, Schaktachtinskaya and Vaidova between 1948 and 1969 are in Azerbaidzan, Kurashvili and co-workers, Chiaberashvili, Dzaparidze and Dzavelidze in the period between the years 1949 and 1989 studied echinostomes in Georgia, Kuprianova-Scakhmatova who examined adult and larval echinostomes and their hosts in Russia and Kirgizia and Egizbaeva done similar studies in Kazakhstan.

The investigations on the echinostomes in Asia started in the beginning of the twentieth century, with the record by Garrison (1908), who reported echinostomes in humans from the Philippines. Later, in the period between the years 1911 and 1915, the morphology and biology of adult echinostomes in Indochina and Japan were studied by Leiper, including the description of *E. malayanum* as a human parasite (Leiper, 1911). In addition to these data, are findings in the period between 1915 and 1922 of when Lane described adult echinostomes in mammals and humans in Asia (see Lane, 1915). One of the first records by the Japanese school for the investigation of echinostomes in this period is that of Tanabe (1922, 1926) who described several adults of echinostomes in Japan. Between 1917 and 1926 many authors published data on findings of adult parasites in Japan, which strengthens the development of the Japanese school investigating echinostomes. Among these authors are Ando and co-workers, who in 1922 presented data about biology and hosts of adult echinostomes from Japan (Ando and Ozaki, 1923; Ando and Tsuyuki, 1923). Houdemer (1938) focused his investigations on the adults parasitizing wild and domestic animals from Vietnam. Additionally Asada (1926) presented data concerning adult worms and their hosts in Japan. In this period of development of the Japanese school investigating echinostomes, there are many data about studies on their larval stages and life cycles, including these by Muto (1921), Miki (1923) and Tsuchimochi (1924) who presented morphological data biological characteristics for echinostomes from Japan. Morphology and life cycle of adults and larval echinostomes from China and Philippines have been studied by Tubangui (1922, 1932). Morishita (1929) studied the echinostomes from birds in Formosa (Japan). A relatively long is the period in which Yamaguti studied the helminth species in Japan, including also members of the family Echinostomatidae between the years 1933 and 1975 when Yamaguti studied many helminth species in Japan, including also members of the family Echinostomatidae. As a result of the obtained information concerning their morphology, hosts and life cycle data, reorganization and two systems of echinostomes were published (Yamaguti, 1958, 1971) that have served for a long time as the basis for the classification of the echinostomes. In Australia, the echinostome fauna was studied by Johnston (1913, 1916) and Johnston and Angel (1949).

In the Americas, the investigations on echinostomes during the first half of the 20th century were mainly focused in the USA. Cort (1914) described *Cercaria trivolvis* released by specimens of *Helisoma trivolvis* in Douglas Lake, Michigan. Moreover, this author also described *C. reflexae* and *Cercaria* sp. Barker (1915, 1916) examined the adult echinostomes obtained from rodents and described several species such as *Echinoparyphium contiguum*, *Echinostoma coalitum*, *E. armigerum* and *E. callawayensis*. The first revision on the echinostomes from North America was published by Ward (1917). Johnson (1920) was the first to make observations on the life cycle of an echinostome. He was supposedly working with *E. revolutum* and he studied the morphology and the development of several larval stages in the laboratory. During this stage of the American school many other investigations were developed, including those by McCoy (1928) publishing data concerning the life cycle of echinostomes from Missouri, Fallis (1934) concerning the infectivity of echinostome metacercarial cysts collected from tadpoles in goslings, Miller (1936) who presented data on the morphology, biology of echinostome cercariae in North America and by Stunkard (1938) who presented additional data on adults and larval echinostomes from the USA. Beaver (1937) presented the most complete study up to that time on the morphology and biology of an echinostome. His experimental study on *E. revolutum* has been followed by several researchers during many years of investigations on the morphology and life cycle of other members of the family.

Meanwhile, in South America investigations on echinostomes started with the studies by Travassos and co-workers in Brazil beginning in 1922 and continued until 1951 (see in Travassos *et al*., 1969). During the same period, Lutz (1924) studied the adult and larval echinostomes in Brazil.

Second half of the 20th century (period from 1950–1990)

In the second half of the 20th century, the studies on the systematics and phylogeny of the echinostomes continued but several groups started to investigate other aspects of the echinostomes such as the immunology of the infections.

In Russia, several studies were focused on the echinostomes of the Black Sea area (Leonov 1956 and 1961 Ryzhikov 1957 and 1983). Iskova between 1964 and 1985 studied in detail the morphology, biology and hosts of adults from birds in Ukraine and from birds in the Caspian and Black Sea regions. This author included five valid species of 37 collar spined echinostomes (the so-called "*revolutum*" group) and presented a key based on adult morphology (Iskova, 1985). Bykhovskaya-Pavlovskaya (1954), Ginetsinskaya and co-workers (Ginetsinskaya and Dobrovolski, 1964) and Belopolskaya (1952, 1954) (and studied the morphology, biology, ecology and hosts of adult and larval echinostomes in fishes and birds and invertebrates in the former USSR. Similar investigations were done by Nevostrueva between 1953 and 1965 (Nevostrueva, 1953) and by Smogorjevskaya (1976) who published a monograph on echinostomes from Ukraine. Sudarikov in the period 1950–1994, Karmanova in the period 1959–1976 and and Kosupko between 1966–1972 studied the life cycles and morphology of adult and larval echinostomes in the former USSR; (Sudarikov, 1950; Kosupko, 1969, 1971a, b, 1972; Karmanova, 1971, 1974; Sudarikov and KarmanovA, 1977). Shishov and co-workers, between 1983 and 1986 studied the aminergic structures of the nervous system of echinostome rediae, cercariae and metacercariae (see in Shishov, 1991). Nasincova (1986, 1991) described the life cycle of *E. revolutum* and *E. bolschewense* in the former USSR. Other authors such as Kiseline, Grabda-Kazubska, Barsiene and Moczon studied the nervous system and karyotype of the echinostomes (Grabda-Kazubska and Moczon, 1988; Grabda-Kazubska and Kiseliene, 1989; Barsiene, 1993; Barsiene and Kiseline, 1991).

Aside from Russia, in Eastern Europe several authors have worked with echinostomes. For example, Zdarska (1963, 1964) carried out series of investigations on the ultrastructure and life cycles of echinostome larvae from former Czechoslovakia. In Bulgaria, several authors developed a large amount of work during this period. Vassilev and co-workers between 1958 and 1996 carried out in Bulgaria studies on the biology, hosts and life cycles of echinostomes from Europe and Asia (see, for example, Vassilev and Kanev, 1979, 1981; Vassilev *et al*., 1982a, b). Additional investigations on echinostomes have been done by Mihov and co-workers on protein fractions in adults (Vassilev *et al*. 1984), by Mutafova and co-workers on karyotypes of echinostomes (Mutafova and Kanev, 1983, 1986), by Dragneva and co-workers on antigen similarities between echinostomes and their invertebrate hosts, by Poljakova and co-workers – scanning electron microscopy investigations on adult and larval echinostomes (Poljakova-Krusteva, and Kanev, 1983), by Gorchilova and co-workers -ultrastructural and enzymocytochemical studies with adult and larval trematodes (Gorchilova and Kanev, 1984, 1994) and by Dimitrov and co-workers on the argentophilic structures of echinostome miracidia, rediae and cercariae (Dimitrov *et al*., 1985, 1997; Dimitrov and Kanev, 1992).

Kanev and co-workers between the years 1977 and 2009 studied adult and larval echinostomes from Europe, Asia, Africa, Australia, North and South America and in 1990 published in Bulgaria Check lists of *Echinis*, *Echinostoma* and Echinostomatidae (Kanev, 1990). As a result of the above mentioned studies in Bulgaria, this author focused his studies on the problematic systematics of the group of *Echinostoma* with 37 spines in the cephalic collar or "*revolutum*" group (see Kanev, 1985, 1994; Kanev *et al*., 1995a, b and references therein). These studies covered worldwide species and were based on morphological, biological and ecological features. These authors re-examined and redescribed three species and concluded that only five species may be considered valid in the "*revolutum*" group: *E. revolutum*, *E. echinatum* (Zeder, 1803), *E. trivolvis* (Cort, 1914), *E. jurini* (Skvorozov, 1924) and *E. caproni* Richard, 1964. The conclussions of these authors have been widely accepted and, for a time have constituted the basis of diagnosis in the "*revolutum*" group. The conclusions by Kanev and co-workers were revised in detail by other Bulgarian researchers such as Kostadinova and coworkers (Kostadinova, 1995; Kostadinova *et al*. 2000).

In France, several authors studied the echinostomes during this period. Richard and coworkers described *Echinostoma caproni* as a new species and its life cycle (Richard, 1964; Richard and Brygoo, 1978) using materials from Madagascar. This species is currently extensively used as an experimental model. Also in France, the revisions on the cercarial chaetotaxy of several trematodes including the echinostomes should be mentioned (Richard, 1971; Bayssade-Dufour, 1978). Particular mention should be made to the Danish Bilharziasis Laboratory in Copenhagen. Members of this group can be considered as the pioneers of the studies of immuniobiology of the echinostome infections. A member of this group (N.O. Christensen) published many papers on the immunological aspects of the echinostome infections in mice and the inter-specific interactions with other parasites in co-infections (Bindseil and Christensen, 1984; Christensen *et al*., 1984, 1985). Other researchers from the same laboratory, such as Simonsen, Frandsen Nansen, Andresen, Odaibo among others, followed these studies publishing several works on this topic.

In the Americas, other authors such as Stunkard and Najarian continued working on echinostomes, especially the systematics and life cycles (see, for example, Najarian, 1952, 1954; Stunkard, 1960) but of particular importance is the work by Fried and co-workers. Fried can be considered the most relevant author in the field of echinostomes. This author has developed an extensive career in this field that started in 1961 and continues today. Professor Fried has established collaborations with scientists worldwide and published more than 300 papers on echinostomes including topics such as morphology, systematics, biology and life cycles, population dynamics, immunology and pathology, genetics and proteomics. Most of these papers are compiled in several reviews (Huffman and Fried, 1990; Fried and Huffman, 1996; Fried and Graczyk, 2004; Toledo *et al*., 2009) and two books (Fried and Graczyk, 2000; Fried and Toledo, 2008).

During the same period between 1949 and 1983 were the investigations carried out by Lie and co-workers who worked extensively on the life cycles, synergistic and antagonistic interactions, host-parasite relationships and various other studies with adult and larval echinostomes from Asia, Africa and South America (see, for example, Lie, 1963, 1964, 1966, 1968; Lie *et al*., 1968), including the description of several new species (Lie and Basch, 1966, 1967; Lie and Umathevy, 1965a, b; Lie *et al*., 1975).

Late 20th century and early 21th century

Late 20th century and early 21th century have been characterized by the use of new technologies applied to the study of echinostomes. This fact has led to echinostomes becoming an experimental model extensively used during this period by different groups for a wide range of purposes such as studies on systematics and host-parasite relationships, including studies on treatment, immunology, genomics and proteomics among others.

As mentioned above, the systematics of the echinostomes have long been confused because of both the morphological similarity between the members of the group and/or the inadequate and poor specific diagnosis of several newly established taxa. During the late 20th century and early 21th century several efforts have been made to clarify the systematics of the group using molecular-based technologies as a tool. The application of this technique to the study of echinostomes started in the late 20th century. The random amplification of polymorphic DNA (RAPD) using PCR was used to identify closely related species (Fujino *et al*., 1995; Petrie *et al*., 1996; Cheng *et al*., 1999). Similarly, Grabda-Kazubska *et al* (1998) used ITS-1 markers from rediae and cercariae to differentiate several species belonging to different genera of Echinostomatidae.

Morgan and Blair (1995, 1998a, b) studied the systematics of several echinostomes using ITS sequences, mtDNA and the ND1 gene. Although the results obtained by these authors were consistent with the hypothesis of the species boundaries by Kanev and co-workers, the results obtained by Sorensen *et al*. (1998) invoked uncertainty with respect to the materials used in previous studies. Apart from other factors, these discrepancies may be the result of misidentification of the materials studied.

In this context, Kostadinova *et al*. (2003) performed an integrative analysis for attempting the phenotypical identification of the materials and adding further ND1 sequences from 17 European isolates of Echinostomatidae. The data-set presented by these authors showed a significant phylogenetic structure for the first time in the group. This results served to clarify the phylogenetic relationships between several common genera of Echinostomatidae (*Echinostoma*, *Echinoparyphium*, *Hypoderaeum*, and *Isthmiophora*). The phylogenetic trees from the ND1 data helped to clarify the genetic adscriptions of all isolates and confirmed the morphological identifications. Additionally, the most recent studies have evidenced the existence of "cryptic" species within the group that highlight the need for further analyses of patterns of interspecific variation based on molecular and morphological evidence (Detwiler *et al*., 2010, 2012; Georgieva *et al*., 2013).

The host-parasite relationships in the first intermediate host have also been extensively studied using echinostome infections during this period. Extensive work has been done in relation to the host-finding processes of free-living parasite larval stages, especially by Nollen and co-workers and Haas and co-workers. These studies have allowed workers to identify the signals that determine the location and identification of the host by the miracidia and cercariae (Haas, 1994; Haas *et al*., 1995; Korner and Haas, 1998a, b; Meece and Nollen, 1996; Haberl *et al*., 2000; Loy *et al*., 2001; Muñoz-Antoli *et al*., 2003).

The immune response of snails against echinostome infections has also been studied in detail during this period with special emphasis by Loker and co-workers in the USA and Coustau and co-workers in France. The interest in this topic comes from the fact that several species of *Echinostoma* share the first intermediate host (*Biomphalaria glabrata*) with species of *Schistosoma*. Several studies in the late 20th century demonstrated that snails are not passive hosts for echinostomes and can manage and eliminate the infections (Adema *et al*., 1994; Loker and Adema, 1995). These studies allowed workers to define several mechanisms involved in the snail defense against pathogens. For example, it was shown using echinostomes that the *B. glabrata* immune system relies on both humoral and cellular responses that cooperate in the recognition and elimination of invaders, with the haemocytes being the major effector cells (Coustau and Yoshino, 1994; Yoshino and vasta, 1996; Lardans and Dissous, 1998). In the 21th century, studies have been focused on the identification of the parasite and host proteins implicated in the interaction between both organisms. For example, Bouchut *et al*. (2006a, b, 2007) analyzed the proteins differentially expressed between *B. glabrata* susceptible and resistant strains. Guillou *et al*. (2007) focused their study in the transcripts that are regulated during the parasite encapsulation identifying several genes of interest. Another focus of interest has been the fibrinogen-related proteins (FREPs) that are capable of binding miracidia, sporocysts, rediae of echinostomes and their excretory-secretory products (see, for example, Hertel *et al*., 2005). Proteomics of the *E. caproni-B. glabrata* system also has been another topic thoroughly studied by Coustau and co-workers. Analysis of the proteome of the sporocysts of *E. caproni* has shown a marked abundance of proteins that may protect the parasite from oxidative damage (Guillou *et al*., 2007).

In Switzerland, Keiser and co-workers are doing extensive work using *E. caproni* as a model in studies on chemotherapy and metabolic profiling. These authors have performed a number of in vivo (using mice as definitive host) and in vitro studies with *E. caproni* as the drug discovery tool. They have assessed the anthelmintic properties of different medicinal plants and compounds which have allowed them to define several drug development candidates (Keiser *et al*., 2006a, b, c; Saric *et al*., 2008; Keiser 2010; Ferreira *et al*., 2011; Kirchhofer *et al*., 2011; Panic *et al*., 2013). Moreover, these workers have started the study of metabonomics in helminth infections using *E. caproni* as an experimental model (Saric *et al*., 2008).

In Spain, Toledo and co-workers have extensively worked on echinostomes beginning in 1997. Initially, the work of that group was devoted to the systematics and life-cycles of these parasites in France (Esteban *et al*., 1997; Toledo *et al*., 1998a, b, 2000; Muñoz-Antoli *et al*., 2000). In the 21th century, this group has used the *E. caproni*-rodent model to study the host-parasite relationships in intestinal helminth infections with emphasis on the factors determining worm rejection or, in contrast, the development of chronic infections. These studies have allowed these workers to delimit the immunological parameters that determine the outcome of the infection providing essential new insights in the factors determining the natural expulsion of intestinal parasitic helminths from their hosts (Toledo *et al*., 2006; Muñoz-Antoli *et al*., 2007; Sotillo *et al*., 2007, 2010a; 2011; Trelis *et al*., 2011, 2013; Cortés *et al*., 2014). Recently, Muñoz-Antoli *et al*. (2014) reported the regeneration of the intestinal tissue as a major effector mechanism responsible for the early expulsion of echinostomes and, probably, other intestinal helminths. Apart from these results, this group also has characterized several antigenic proteins and post-traslational modifications that can modulate the outcome of the infection (Bernal *et al*., 2006; Marcilla *et al*., 2007; Higón *et al*., 2008; Sotillo *et al*., 2008, 2010b, 2014; Muñoz-Antoli *et al*., 2014). Recently, Garg *et al*., (2013) presented the first transcriptome of the adult stage of an echinostome and compared it to those of other trematodes revealing similarities in transcription for molecules inferred to have key roles in parasite-host interactions. Of particular interest was the finding by Marcilla *et al*. (2012) who demonstrated for the first time the existence of exosome-like vesicles in parasitic helminths.

Other groups that should be mentioned in relation to their work on echinostomes during the late 20th and early 21th century are those from the Yonsei University in South Korea and the Oswaldo Cruz Institute in Brazil. The group from Yonsei University has done extensive work on the immunobiology of infections with *E. hortense* (Kim *et al*., 2000; Lee *et al*., 2004, 2009; Cho *et al*., 2007; Ryang *et al*., 2007). The group from the Oswaldo Cruz Institute in Brazil has studied the life-cycles and population dynamics of echinostomes in Brazil (Maldonado *et al*., 2001a, b, 2003; Pinheiro *et al*., 2004a, b, 2005).

A brief history of human echinostomiasis

It has been known for a long time that echinostomes parasitize humans. Human infections with echinostomes were demonstrated in Brazil in pre-Columbian period. Paleoparasitological studies have demonstrated the presence of *Echinostoma* eggs in coprolites from a mummified human body in Brazil dated 560 ± 40 before present, that showed similarities with *E. paraensei* and *E. luisreyi* (Sianto *et al*., 2005; Leles *et al*., 2014). However, the first report of human echinostomiasis in living populations was that of Garrison (1908) who found eggs of an echinostome in the feces of five prisoners in Manila (the Philippines), and 21 adult worms were recovered from one patient after treatment. Adult worms were identified as *Echi-*

nostoma ilocanum. Thereafter, several records were made in Asia. For example, Majima (1927) found echinostome infections in humans caused by *E. macrorchis* and Hirazawa (1928) reported a human infection with *Echinoschasmus perfoliatus* in Japan. Anazawa (1929) reported, in Taiwan, the first human infection with *E. revolutum*.

Of particular interest were the findings by Sandground, Bonne and co-workers since their work constituted the first epidemiological approach to human echinostomiasis. Cases of echinostomiasis in humans, discovered during autopsies, were reported by Sandground and Prawirohardjo (1939). Most of the worms recovered were *E. ilocanum*, but some specimens of *E. recurvatum and E. revolutum* were also identified. Sandground (1939) subsequently reported that echinostomes were frequently recovered from field rats near Jakarta. In the same paper was reported the discovery of an endemic focus of E. *ilocanum* in inhabitants of a rural colony for the insane near Jakarta. Bonne and Sandground (1939) and Sandground and Bonne (1940) found a highly endemic focus of *E. echinatum* (= *E. lindoense*) transmission in Central Sulawesi. Infection rates in residents of the Lindu Valley varied from 24 to 96%. *E. malayanum* also was found in humans in Sumatra (Bonne, 1941). Currently, human echinostomiasis, attributed to at least 20 species, is endemic to Southeast Asia and the Far East. Most of these endemic foci are localized in China, India, Indonesia, Korea, Malaysia, Philippines, Russia, Taiwan, and Thailand. Moreover, occasional cases have also been reported in other countries (Graczyk and Fried, 1998; Chai, 2008; Toledo *et al*., 2012). Several groups have devoted considerable work to study the epidemiology of human echinostomiasis. Chai and co-workers have studied in detail echinostomiasis in Southeast Asia with emphasis in the Republic of Korea. Most of the work of these authors has been complied in several reviews that give an idea of the volume of work carried out by this group (Chai and Lee, 1990, 2002; Chai, 2007, 2008).

Concluding Remarks

In the present manuscript, we provide an overview of the evolution of the research on echinostomes. Over the course of time, studies have evolved from the most basic aspects of parasitology to the frontline of parasitology in several areas. There are several reasons that help to explain this progress. In spite of the problems involved in the systematics of echinostomes, they still serve as the subject of basic studies to gain further insights in methodologies used to clarify the taxonomy and the phylogeny of helminths. Otherwise, their suitability as experimental models has allowed for the application of the most novel technologies in studies of several topics of great interest in studies on the host-parasite relationships. The present review should serve to gain a better understanding of this group of digeneans as experimental models and their potential role for future novel research in the field of parasitology.

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