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Historical Aspects of Echinococcosis

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Abstract

Echinococcosis is a zoonosis whose history dates back to antiquity. This article provides an overview on the general history of echinococcosis, including the elucidation of Echinococcus life cycles and the long controversy on the aetiology of the cystic and alveolar forms of echinococcosis (CE and AE), lasting about 100 years since the middle of the 19th century. Furthermore, selected historical aspects of some fields of echinococcosis research are discussed and compared with our current knowledge, such as geographic distribution and epidemiology of CE (Echinococcus granulosus) and AE (Echinococcus multilocularis), clinical aspects and pathology, diagnosis in humans and animals, treatment (with focus on chemotherapy), control and basic research. A short paragraph is devoted to the neotropical forms of echinococcosis, caused by Echinococcus vogeli and Echinococcus oligarthrus. In this context the achievements of some ancestral pioneers of echinococcosis research are particularly highlighted and appreciated. Finally, the role of associations, international organizations (World Health Organization and others) and international working groups in echinococcosis research and control is briefly outlined. The retrospective reveals both the admirable achievements of our ancestors and the scientific progress of more recent times. But, it also shows the gaps in our knowledge, skills and resources that we need to control or even eradicate echinococcosis.

1. INTRODUCTION

Although echinococcosis has a long history dating back to ancient times, it is still a relevant zoonosis today with considerable socioeconomic impact, affecting humans in many parts of the world (WHO, 2001a; Craig and Pawlowski, 2002; Eckert and Deplazes, 2011; Torgerson and Macpherson, 2011; Vuittton et al., 2015). Here, we highlight selected historical aspects of some fields of echinococcosis research, with examples of what contributions our ancestors have made to our current knowledge which has continuously grown, especially since the 19th century and what changes have occurred over the years. The reader is also referred to
Echinococcosis is a zoonosis involving carnivores as definitive and a broad spectrum of mammalian species as intermediate hosts. Humans, monkeys and some other mammals can be affected as aberrant hosts. Currently, four forms of echinococcosis are distinguished (WHO, 2001a; D’Alessandro and Rausch, 2008) (Table 1). Cystic and alveolar echinococcosis (CE and AE), the most important forms with the widest geographic ranges, are the focus of this article. CE is also called hydatid disease (Greek: *hydatis*: water bladder).

**2. ECHINOCOCCUS GRANULOSUS AND ECHINOCOCCUS MULTilocULARIS**

2.1 General historical aspects

2.1.1 Early knowledge of hydatids

The metacestodes of *E. granulosus* are bladders (cysts) of variable and often large size filled with clear liquid and are called ‘hydatids.’ The first indications of hydatids date back to antiquity and stem from Hippocrates (circa 460–377 BC) who wrote in his aphorisms (VII, 55): ‘In those whose water stuffed liver opens into the omentum, the belly is filled with water, and they die.’ (Neisser,
Galen (129—~200 BC) regarded the liver as the main site of hydatids and mentioned their occurrence in slaughter animals (Hosemann, 1928). Around 50 AD, Aretaeus (or Areaios) of Cappadocia described in his work ‘De causis et signis morborum’ different clinical entities of people. He noted that in patients with ascites, numerous small, fluid-filled blisters may be present in the abdomen and that some liquid emerges when an abdominal puncture is attempted with a trocar (Neisser, 1877). In the following periods, the presence of hydatids in animals and humans was repeatedly reported in the literature, for example, in the 16th and 17th century. Wolckerus described an alleged abscess, from which 300 hydrous bladders deflated (Neisser, 1877; Langenbuch, 1890). In 1679 Théophile Bonet (1620–89) in Geneva published a summary of the pathological knowledge in a work entitled ‘Sepulchretum sive anatomia practica’ ('burial ground or practical anatomy') (Ackerknecht, 1989), containing hints on some patients harbouring hydatids (Langenbuch, 1890).

2.1.2 Knowledge on the nature of hydatids

Until the early modern age, the true nature of hydatids remained unknown, and they were regarded before that time as degenerated glands, as accumulations of serum or mucus between laminar cell layers or as descendants of so-called ‘milk vessels’ or blood vessels (Langenbuch, 1890). First indications of the animal nature of metacestodes arose from observations of Francesco Redi (1626–97) who recognized in 1684 in Florence that cysticerci (metacestodes of *Taenia* spp.) are able to move like animals (Grove, 1990). In the following year 1685, Philip Jacob Hartmann (1648–1707)—Professor of Medicine and History of Medicine at the University of Königsberg/Germany (now Kaliningrad/Russia)—confirmed the animal nature of cysticerci, describing a small, spherical structure that was connected with the metacestode bladder. Apparently, he had described a *Cysticercus tenuicollis* with scolex, the metacestode of *Taenia hydatigena* (Enigk, 1986). These observations were unknown to Edward Tyson (1650–1708) a doctor in Oxford. He also had observed the motility of *C. tenuicollis* and reported in 1687 to the Royal Society that ‘hydatids in animals are a sort of living creatures,’ which he called ‘lumbrici hydropici,’ thus providing a clue for a possible link with ‘worm’ parasites (Grove, 1990). Peter Simon Pallas (1741–1811) born in Berlin, allocated the hydatids as a discrete group to the ‘bladder worms’ and described in his medical dissertation in 1760 (submitted to the University of Leiden/The Netherlands) ‘small bodies’ (brood capsules) on the inner wall of the bladders (Neisser, 1877; Enigk, 1986). In
these bodies, the priest John August Ephraim Goeze (1731–93) in Quedlinburg/Germany recognized in 1782 tapeworm scoleces (Enigk, 1986). In 1801 Carl Asmund Rudolphi (1771–1832) (Dr phil. 1773 and Dr med. 1795 at the University of Greifswald/Germany) introduced the name ‘Echinococcus’ to zoology (Rudolphi, 1801) (Figs 1 and 2).

2.1.3 Elucidation of the life cycle of Echinococcus granulosus

2.1.3.1 Development in final hosts

In 1688 Johann Jacob Wepfer (1620–95), physician in Schaffhausen/Switzerland, had observed that a tapeworm stage occurring in the liver of


mice (subsequently called *Strobilocercus fasciolaris*) exhibited features of an intestinal cat tapeworm, which was then called ‘latis lumbricus intestinorm’ (today *Taenia taeniaeformis*). Thus Wepfer was the first to make a link between the intestinal stage of tapeworms and its cystic stage developing in internal organs (Enigk, 1986; Grove, 1990) (Fig. 3).

Approximately 150 years later, in 1842, the Dane Johannes J.S. Steenstrup (1813–97)—Lecturer of Zoology and Mineralogy at the Academy in Sorø on Zealand and later Professor at the University of Copenhagen—formulated his theory on alternations of generations. In this sense, he regarded the cystic stages as early forms in the development of helminths that were unknown to him (Grove, 1990). In 1845 Felix Dujardin concurred with this view in France. He infected dogs and cats experimentally with cysticerci, but he was reluctant to publish his results, which resulted in Küchenmeister in Germany preempting him with publication of his data (Enigk, 1986).

After graduation in 1846 as a medical doctor at the University of Leipzig/Germany, Gottlob Friedrich Heinrich Küchenmeister (1821–90) settled down as a medical practitioner and obstetrician in Zittau and from 1859 in Dres (Enigk, 1986). In 1851 during his time in Zittau, he fed *Cysticercus pisiformis* (metacestodes of *Taenia pisiformis*) to four red foxes and isolated from their intestines young tapeworms with scoleces identical with those of the cysticerci (Küchenmeister, 1851; Enigk, 1986). With this, Küchenmeister had detected the life cycle of taenid tapeworms, but this basic observation by a medical practitioner was heavily criticized by Carl Theodor Ernst von Siebold (1804–85) who was Professor of

Figure 3 J.J. Wepfer (1620–95). With permission of Stadtarchiv Schaffhausen, Switzerland, 07.01.2016.
Physiology at the University of Breslau/Germany (now Wrocław/Poland) since 1850 (Enigk, 1986). Later, however, von Siebold followed the example of Küchenmeister. In 1852 he infected several dogs with protoscoleces from hydatid cysts and found in their small intestines tapeworms that were a few millimetres long at 27 day post infection (p.i.) composed of a scolex and two to three proglottids (von Siebold, 1853). For the first time, he had obtained experimentally E. granulosus which had been described previously by Batch, 1786, Zeder, 1803, and Rudolphi, 1801 (cit. in Enigk, 1986). Soon thereafter, these findings were confirmed by several authors (Figs 4 and 5).


However, it remained still unknown, how metacestodes in intermediate hosts develop from intestinal tapeworms of carnivores. Küchenmeister (1853) infected dogs with metacestodes of *Taenia multiceps*, isolated the tape-worm eggs and transferred them to a sheep, in which he later found young metacestodes. Finally Rudolf Leuckart (1822—98) infected piglets with eggs of ‘*Taenia echinococcus,*’ obtained from a dog and detected 4 weeks later in the livers of these animals small vesicles (0.25 to 0.35 mm) showing a laminated layer (‘glashelle Kapsel’). He also depicted and described in detail the further development of these stages including the formation of brood capsules and protoscoleces (Leuckart, 1863).

**Rudolf Leuckart**, born in Helmstedt/Germany, had studied medicine in Göttingen. He was first associate Professor of Zoology in Giessen and then appointed in 1869 as a Professor of Comparative Anatomy at the University of Leipzig. By his profound and broad-based zoological and parasitological work, R. Leuckart had a long-lasting impact on the development of biological sciences and parasitology in the 19th century and beyond (Enigk, 1986) (Figs 6 and 7).

2.1.3.2 Development in intermediate hosts, cyst formation and secondary echinococcosis

After Leuckart’s observations (see above), it was discussed for some time how the oncospheres migrate in the intermediate host’s body. A few authors had speculated that oncospheres, hatched in the gastrointestinal tract from the eggs, may be incorporated passively like ‘foreign bodies’ (Hosemann,
Dévé in France and Dew in Australia were the first to show that the oncopheres penetrated actively the intestinal wall, entered small portal veins and were subsequently carried in the bloodstream to the liver. Both Dew (1925) and Dévé (in Hosemann, 1928) had observed larvae in portal veins of the liver a few hours after experimental infection of pigs. It was concluded that most larvae remain in the liver, but a few of them may pass the liver ‘filter’ and are transported to the lung or other organs. This view was consistent with the sites of cysts in the human body, predominantly localized in the liver and less frequently in other organs [according to Dévé (in Hosemann, 1928): 74.5% liver, 8.6% lung and pleura, 2.3% spleen, 2.1% kidneys, 6.2% muscles].

Another important aspect of practical and basic interest was the aetiology of secondary echinococcosis which may occur in body cavities of human patients following cyst rupture. In 1898 von Alexinsky (in Hosemann, 1928) had experimentally demonstrated that intraperitoneal injection of ‘hydatid sand’ (containing protoscoleces) resulted in cyst formation. Several years later, Dévé confirmed these findings by injecting hydatid sand intraperitoneally to rabbits with the result that 23 of 32 of his experiments were positive. Furthermore, Dévé could clearly demonstrate by histological studies that cysts can arise from protoscoleces (Dévé, in Hosemann; Dévé, 1902, 1946).

Félix Dévé (1872–1951) studied medicine in Paris. In 1990 he began his long series of investigations on echinococcosis and presented in 1901 his thesis on secondary echinococcosis (Dévé, 1901). In 1942 he was appointed as Professor of Clinical Medicine in Rouen. He published three books and more than 300 articles on hydatid disease (Grove, 1990).

Harold Robert Dew (1891–1962) studied medicine at the University of Melbourne and graduated in 1914. In 1920 he became a fellow of the
In 1852 Ludwig Buhl (1816–80), pathologist at the University of Munich/Germany, had diagnosed in a human liver an uncommon liver tumour which he initially called ‘alveolarcolloid’ (‘colloid cancer’) but recognized it in 1854 as a deformed Echinococcus lesion (Buhl, 1855). In 1855 Rudolf Ludwig Virchow (1821–1902) presented to the ‘Physicalisch—Medizinische Gesellschaft’ in Würzburg a detailed report on ‘Die multiloculäre, ulcerierende Echinokokkengeschwulst der Leber’ (multilocular, ulcerating Echinococcus tumour), referring to cases described by Buhl and some other authors (Virchow, 1856). At that time, Virchow was Professor of Pathology at the University of Würzburg where he developed his famous concept of cellular pathology (Enigk, 1986) (Fig. 8).

2.1.5 Controversy on the aetiology of cystic and alveolar echinococcosis
With the identification of the ‘alveolarkolloid’ as a form of echinococcosis two disease patterns were recognized in the mid-19th century, which are
called today cystic echinococcosis and alveolar echinococcosis (CE) and (AE), respectively. However, it was unclear whether these two forms were caused by a single or by two different *Echinococcus* species. In the following period, a lively debate developed in which ‘unicists’ faced a group of ‘dualists.’ The unicists, among them L. Buhl, R. Virchow, G. F. H. Küchenmeister, R. Leuckart, F. Devé and H. R. Dew, regarded *E. granulosus* (then called *Taenia echinococcus* or *T. echinococcus cysticus*) as the cause of human CE and AE but assumed that structure and growth characteristics of the metacestodes are widely variable, depending on mechanical and physiological factors in the human host tissue (Hosemann et al., 1928). These and other arguments did not convince the dualists who embraced different *Echinococcus* species as causative agents. A. Morin (1875) was apparently one of the first who considered a dualistic conception in his thesis at the University of Berne/Switzerland (Morin, 1875). His view was supported by other authors, including Adolf Posselt (1867–1936), Professor of Internal Medicine at the University of Innsbruck/Austria (Fig. 9).

In 1901/1902 Posselt was the first to provide clear experimental evidence that human AE is caused by *E. multilocularis* (then called *Taenia echinococcus alveolaris*). He isolated from a human patient alveolar parasite tissue containing numerous protoscoleces and infected a parasite-free dog. After 49 days, he found in the intestine numerous small tapeworms with typical morphological features of the adult stages of *E. multilocularis* (Posselt, 1928). In addition to the results of the feeding experiment, Posselt presented many other plausible arguments (parasite morphology, pathology, histology, clinical signs,
geographic distribution etc.) in support of the dualistic conception, summarized in a classical treatise ‘Der Alveolarechinokokkus und seine Chirurgie’ (the alveolar echinococcus and its surgery) (Posselt, 1928). Photos in this publication indicated that the structure of the gravid uterus of *T. echinococcus alveolaris* clearly differs from that of *T. echinococcus cysticus* (= *E. granulosus*) from Australia, and drawings showed morphological differences of the scolex hooks (Posselt, 1928). Fifty six years later, Vogel (1957) could reexamine the specimens from Posselt’s feeding experiment and recognized ‘all characteristics’ of *T. echinococcus alveolaris* (= *E. multilocularis*). The controversy between ‘unicists’ and ‘dualists’ had persisted for approximately 100 years. Even in 1953, Dew (cited in Vogel, 1957) has stated with regard to the various forms of echinococcosis in humans and domestic animals: ‘If the essential unity of the hydatid species is admitted, and I think all workers now admit this, all the above forms, simple and bizarre, are different forms assumed by the larval stage of the same parasite.’ However, a new chapter of the story had already been opened in 1951 by the work of Rausch and Schiller in Alaska (see Section 2.1.6).

### 2.1.6 Elucidation of the life cycles of *Echinococcus sibiricensis* and *Echinococcus multilocularis*

With the successful infection of a dog with fertile alveolar metacestode material isolated from a human patient in 1901/1902 Posselt had already elucidated part of the life cycle of *E. multilocularis* (Posselt, 1928). However, many questions remained open until Robert Rausch and E. L. Schiller published the results of their pioneering studies on alveolar echinococcosis of Inuits in Alaska (Rausch and Schiller, 1951, 1954, 1956). They identified arctic foxes (*Alopex lagopus*) and sledge dogs as definitive hosts of a new *Echinococcus* species which they described as *E. sibiricensis*, found alveolar metacestodes in rodents (field vole and red-backed vole), succeeded in infecting experimentally microtine rodents with eggs of the newly identified *Echinococcus* species, and associated these findings with AE cases in the Inuit population (Rausch and Schiller, 1951, 1954, 1956). Robert L. Rausch (1921—2012) was then a member of the United States Public Health Service at the Arctic Health Research Center in Alaska since 1948 and since 1978 Professor at the Washington State University in Seattle.

In the mid-1950s Johannes Vogel (1900—80), helminthologist at the former Tropical Institute in Hamburg/Germany (inspired by the findings of Rausch and Schiller, as he mentioned in one his publications) conducted epidemiological studies on *E. multilocularis* in Southern Germany (Vogel, 1955, 1957). In the region of the ‘Swabian Alb,’ he found 4 of 10 red foxes infected with *E. multilocularis* and identified voles (*Microtus arvalis*) as natural intermediate hosts. Furthermore, he infected successfully foxes, dogs and
cats with metacestodes from rodents, and rodents (e.g., *M. arvalis*, *Sigmodon hispidus*) with *Echinococcus* eggs isolated from foxes. In an extensive morphological study, he could not find significant differences between specimens of the European *E. multilocularis* and the Alaskan *E. sibiricensis* and proposed for priority reasons the name *E. multilocularis* Leuckart 1863 for both of these parasites (Vogel, 1955, 1957). With this, a 100-year dispute on the aetiology of CE and AE was clarified (Rausch, 1986).

Robert Rausch (1921–2012)\(^1\) acquired a broad education in zoology, entomology, veterinary medicine, parasitology, bacteriology and wildlife biology. He began his research career in 1948 at the US Public Health Service at the Arctic Research Center in Alaska, where he spent 27 years and became Chief of the Infectious Disease Section. After 3 years as Professor of Parasitology at the University of Saskatchewan, he was appointed in 1978 as Professor at the Washington State University in Seattle, School of Medicine, Department of Comparative Medicine. After his retirement in 1992, he continued his work on cestodes and other parasites for many years. His wife, Virginia Rausch, deserves great appreciation for the close scientific cooperation with her husband and her constant support (Figs 10 and 11).

Johannes (Hans) Vogel (1900–80), born in Dresden/Germany, had studied natural sciences in Jena and medicine in Jena and Hamburg from 1919 until 1927. In 1927 he became assistant at the Division of

Helminthology at the Bernhard-Nocht-Institut für Schiffs- und Tropenkranheiten (now Bernhard-Nocht-Institut für Tropenmedizin), and in 1935 he was promoted to Head of the Division as a successor of F. G. H. Fülleborn. From 1963 to 1968, he served as the Director of the Institute (Enigk, 1986). H. Vogel has made major contributions to parasitology, predominantly in cestode and trematode research.

J. Vogel and R. Rausch had cooperated in a collegial manner and acquired a high international scientific and personal reputation through their outstanding work on echinococcosis and other parasitic diseases. More details on the historical development can be found in Enigk’s book ‘Geschichte der Helminthologie im deutschsprachigen Raum’ (history of helminthology in the German speaking area) (Enigk, 1986) and in a review by Tappe et al. (2010a).

3. SPECIFIC HISTORICAL ASPECTS

3.1 Geographic distribution and epidemiology

By the end of the 19th century and the beginning of the 20th century, a remarkable body of knowledge had accumulated on the worldwide geographic distribution and prevalence of echinococcosis in humans and animals, but the overall picture had considerable gaps (Fig. 12).

3.1.1 Echinococcus granulosus and cystic echinococcosis

3.1.1.1 Distribution

Early knowledge of the occurrence of CE in humans was published by Egbert Schwarz, Professor at the University of Rostock/Germany, who had
reviewed the international literature of the period from the middle of the 19th century until the 1920s, published in a remarkable monograph ‘Die Echinokokkenkrankheit’ edited by Hosemann et al. (1928) (Fig. 12). Schwarz (1928) presented information on human CE in South America, with high prevalences in Argentina, Paraguay, Uruguay and Brazil. In Argentina, 970 human cases were registered in 1901. Only sporadic cases were reported in some other South American countries (Chile, Bolivia, Peru, Ecuador, Columbia, Venezuela), in Mexico and North America (United States of America, Canada). Little information was available on the general situation in Africa, but rather high prevalences were known to occur in southern Africa and Algeria, whereas only sporadic cases were recorded in other countries of northern Africa (Morocco, Tunisia, Egypt) as well as in regions of eastern Africa.

In the northern hemisphere, Iceland with its low number of inhabitants (~64,000 in 1849) had very high prevalences of human CE with a range of 104 to 235 cases each year in the period 1896 to 1903, and declining numbers of 105 to 33 in the period 1904 to 1920 (Schwarz, 1928). In other parts of Europe, the CE prevalences were categorized by Schwarz (1928) as medium to high in regions of France, England, Germany, parts of the Netherlands, the Mediterranean region (Portugal, Spain, Italy), Hungary, Dalmatia², Serbia, Greece and some other Balkan states. For example, northern Germany had a high prevalence with 1.98% of human CE cases among 4250 autopsies in Rostock in the period 1861 to 1905. Sporadic cases were reported in

² Historical region of western Balkan.
Belgium, Scotland, Ireland, the Scandinavian area (Denmark, Sweden, Norway), Finland and the Baltic region, Austria and some of the Balkan states (Bulgaria, Romania) (Schwarz, 1928). In Russia, areas in the southern and eastern parts were regarded as especially affected by CE. Apparently, little information existed on the situation in Asia, and only medium prevalences in India and sporadic occurrence in China and Japan are mentioned by Schwarz (1928). On the other hand, the high prevalences in mainland Australia, Tasmania and New Zealand are described in detail. With reference to J. D. Thomas, Schwarz (1928) underlined the great importance of CE in Australia, especially in Victoria, and reported that 200 people died of CE within 14 years (14 per year) in the 1860s, and 52 people in 1884 (Schwarz, 1928).

In summary, Schwarz (1928) had classified several regions as highly endemic for *E. granulosus* and human CE, especially Argentina, Australia and New Zealand, but also parts of northwestern and southern Africa, Iceland, large parts of Europe, except Scandinavian countries, and eastern Russia. Furthermore, he provided some data on CE in livestock and of *E. granulosus* in definitive hosts (e.g., 80% infected dingos in Australia). He pointed out that echinococcosis occurs more or less everywhere and that its detection depends on the awareness of the disease. Studies in the following decades have confirmed Schwarz’s statement showing that *E. granulosus* and CE have a wide range in the northern and southern hemisphere (Matossian et al., 1977; Andersen et al., 1993, 1997; Schantz et al., 1995; WHO, 2001a). According to Torgerson and Macpherson (2011), there is a persistently high burden of CE in many parts of the world with an estimated one million or more people currently suffering from CE globally and financial losses of $2 billion caused by CE in global livestock populations. In some regions, the prevalence is low (e.g., western Europe), whereas other areas are highly affected (e.g., regions in central Asia and China) (Torgerson and Shaikenov 2004, Torgerson and Macpherson, 2011; Torgerson et al., 2011).

3.1.1.2 Epidemiology

In the 1980s/1990s, experimental studies by M. Gemmell and coworkers generated important new basic knowledge for understanding the epidemiology of taeniid cestodes and breaking the ‘epidemiological code’ with the aid of mathematical modelling. This knowledge and data from other authors have been reviewed in several excellent articles (Gemmel and Lawson, 1986; Gemmell et al., 1986; Roberts and Gemmell, 1986; Gemmell and Roberts, 1995; Gemmell, 1997; Gemmell et al., 2001).
Gemmell and coworkers were the first to apply the concept of the basic reproductive rate ($R_0$) to studies on the transmission of *Echinococcus*. They analyzed and quantified the contributions made by the parasites, the definitive and intermediate hosts and the environment to transmission dynamics. The results revealed inter alia that *E. granulosus* and other taeniid cestodes (*T. hydatigena* and *Taenia ovis*) have an overdispersed distribution with only a small number of definitive and intermediate hosts (dogs and sheep, respectively) harbouring a large number of parasites. Compared with *Taenia* species, *E. granulosus* has a much lower biotic potential (potential number of viable cysts developing in the intermediate host per infected dog per day). As acquired immunity to *E. granulosus* in dogs is weak or lacking, it does not play a role in regulating the parasite population. In contrast, immunity to superinfection by *E. granulosus*, *T. hydatigena* and *T. ovis* can be acquired or induced in sheep. Therefore the immune status of intermediate hosts can be a constraint on the parasite population but only under high infection pressure. The parasite population is also influenced by environmental factors, such as climate and egg-dispersal mechanisms. According to Gemmell et al. (2001) for understanding the transmission dynamics and for planning control programmes, the following factors are of great significance: (1) biotic potential of the parasite in the definitive host, (2) acquired immunity as a density-dependent constraint by the intermediate host, and (3) climate as a density-dependent constraint in the free-living egg phase (Fig. 13).

Considerable merit is due to Michael Gemmell (1926–2003), who with his team in Dunedin/New Zealand who collated and analyzed 30 years

![Figure 13](image_url) M.A. Gemmell (1926–2003). Congress photo, collection J. Eckert.
of their experimental infection and transmission data on Taenia spp. and E. granulosus infecting livestock and dogs. For the first time, they were able to build a quantified approach to measure the dynamics of taeniid transmission between mammalian definitive and intermediate hosts. These transmission studies formed the foundation for understanding the epidemiology of E. granulosus and represented an important contribution to the development of detailed concepts for planning, implementation and evaluation of control interventions. M. Gemmell, born in London, studied veterinary medicine at the University of Sydney where he graduated in 1950. In 1958 he became the Director of the Hydatid Research Unit of the Otago Medical School in Dunedin where he worked until the late 1980s. During his career, he was responsible for several major ground-breaking developments, he was an enthusiastic scientist and a competent advisor for national institutions and international organizations [World Health Organization (WHO), Pan American Health Organization (PAHO), Food and Agriculture Organization of the United Nations (FAO) etc.] and has certainly influenced generations of scientists of various fields through his ideas and excellent work. Studies in Gemmell’s area of research are now continued by younger generations (e.g., Torgerson, 2003, 2006; Budke et al., 2005).

3.1.2 Echinococcus multilocularis and alveolar echinococcosis

Compared to E. granulosus, the epidemiology of E. multilocularis is more complex due to its predominantly sylvatic life cycle involving foxes and other wild carnivores as definitive hosts and a large number of small mammals (mainly rodents) as intermediate hosts. Therefore historically, the determination of epidemiological key factors has proven to be more difficult.

3.1.2.1 Human cases of alveolar echinococcosis

After the unequivocal identification of the first human cases of AE in southern Germany in the mid-1850s (Buhl, 1855; Virchow, 1856), further cases were reported in Germany (Vierodt, 1886) and adjacent areas, for example in Switzerland (1858) (Dardel, 1927). Posselt (1928) listed a total of 651 AE cases, which he had collected until Spring 1928, with the following geographic distribution: Germany: 168, Switzerland: 164, Austria: 96, other


4 The published total number is only 600, apparently due to a calculation error in a table.
alpine regions and Mähren\(^5\): 6, France and Italy: each 3, North America: 2, and Russia: 209. Of 440 European cases, 428 (97%) had been diagnosed at that time in Germany, Switzerland and Austria. As early as 1900, Posselt had drawn attention to differences in the geographic ranges of CE and AE in Europe and defined southern Germany, Switzerland, Austrian alpine regions and certain regions in Russia as ‘classical distribution areas’ of AE (Posselt, 1928). Approximately 4% of the cases were found outside this area, namely in Germany up to Hannover and Berlin, in the Baltic region (St. Petersburg/Russia, Tartu/Estonia) and in Warszawa/Poland (Posselt, 1928; Schwarz, 1928). In Russia, AE cases were known to occur in regions around Moscow, Kazan and Tomsk (Posselt, 1928). In Alaska, autochthonous human AE cases were diagnosed in 1947 (Rausch and Schiller, 1951) and in Japan in 1926 (Katsurashima in Suzuki et al., 1993). Posselt (1928) assumed an almost complete separation of the distribution area of AE and CE, but his colleague Schwarz (1928) did not support this view in its strict form. By the end of the 1920s, autochthonous human AE cases were documented only in four central European countries (Germany, Switzerland, Austria, and France), as well as in Russia and Japan (Posselt, 1928; Katsurashima in Suzuki et al., 1993) (Fig. 14).

In the following decades, human AE cases were recorded in many more countries (Eckert, 1996; WHO, 2001a; Vuitton et al., 2003, 2015). Vuitton et al. (2003) listed at least 28 countries with reported human AE cases, including two in North America, 13 in Eurasia and the Middle East, two

\(^{5}\) Mähren = Moravia, eastern part of the Czech Republic.
in Asia, and 11 in (western and central) Europe. Of 559 human AE cases registered by the European Echinococcosis Registry during the period 1996 to 2000 in nine European countries, 539 (96%) were diagnosed in the well-known ‘classical’ endemic area (Austria, Germany, Switzerland) and in France (Kern et al., 2003). Within this area, systematic active case finding studies have only been performed in Switzerland. In this country, the nationwide annual average numbers of new human AE cases were initially low with 0.6, 3.1 and 3.0 cases in the periods 1855 to 1900, 1901 to 1924 and 1926 to 1955, respectively. In the following period 1956 to 2000, these values were higher and varied between 6.6 and 10.0 cases, corresponding to annual incidences per 100,000 population between 0.10 and 0.16 (reviewed in Eckert et al., 1995; Schweiger et al., 2007). These data could be interpreted as a situation of ‘endemic stability.’ However, a distinct increase to 19.2 cases per year was observed in the period 2001 to 2005, resulting in an incidence rate of 0.26, possibly associated with increasing fox populations in rural and urban areas (Schweiger et al., 2007). A similar stable situation existed on Hokkaido/Japan where in the period 1937 to 1997, the average number of new cases per year varied between 4.2 and 11.2 (reviewed in WHO, 2001a).

The People’s Republic of China is a more recently recognized focus with the first human AE cases detected at the end of the 1950s and endemic areas in eight provinces or autonomous regions and high prevalence rates (Vuitton et al., 2003). The global burden of AE has been estimated at over 600,000 Disability-Adjusted Life Years) (Torgerson and Macpherson, 2011).

3.1.2.2 *Echinococcus multilocularis* in definitive and intermediate hosts
Knowledge of the geographic range of AE was initially based on human cases. Dardel (1927) in Switzerland associated human AE with dogs but mentioned that foxes, hares and cattle could possibly play a role in the transmission cycle. Rare cases of multilocular liver echinococcosis in livestock, predominantly in cattle, were initially misdiagnosed as AE by several authors but later identified as CE (Huber, 1861 in Tappe et al., 2010a). The potential role of dogs as definitive hosts of *E. multilocularis* was first substantiated 1901/1902 by the experimental infection of a dog with metacestodes obtained from human AE case (Posselt, 1928).

In the 1950s, arctic foxes (*A. lagopus*) and sledge dogs were identified in Alaska as definitive hosts of *E. multilocularis* (then called *E. sibiricensis*), with voles as intermediate hosts (Rausch, 1951, Rausch and Schiller, 1954, 1956).
The major role played by foxes in the life cycle and epidemiology of *E. multilocularis* was subsequently documented by studies in Europe (Vogel, 1955, 1957, 1961), United States of America (North Dakota) (Rausch and Richards, 1971), the former Soviet Union (Lukashenko, 1971) and Hokkaido/Japan (Yamashita, 1963 in cit Zehyle, 1982). For example, in North Dakota, 67 (70%) of 96 red foxes were carriers of *E. multilocularis* (Rausch and Richards, 1971) and 23% in Hokkaido (Yamashita, 1963 in Zeyhle, 1982). In some of the early European publications, the following prevalence rates of *E. multilocularis* in red foxes were recorded: eastern Switzerland 36% (8/22) (Bouvier et al., 1957), each 40% (4/10) in northeastern Switzerland and southern Germany (Swabian Alb) (Vogel, 1955, 1961), 5% (8/167) in France (Coudert et al., 1970), and 13.5% (598/4441) in southwestern Germany (Zehyle, 1982). Concurrently, rodent species (e.g., field voles in Germany) were identified as natural intermediate hosts (Vogel, 1961).

In studies performed in various geographic regions since the mid-1950s further definitive host species (wolf, coyote, raccoon dog, corsac fox, Tibet fox etc.) of *E. multilocularis* and numerous natural intermediate host species (small mammals, mainly arvicolid and cricetid rodents) were identified (reviewed in Rausch, 1986, Schantz et al., 1995; WHO, 2001a; Vuitton et al., 2003). Furthermore, life cycle patterns were described (Rausch, 1986, 1995) (see below), as well as the sylvatic cycle (wild carnivores—wild intermediate hosts) and the synanthropic cycle (domestic dog—wild intermediate hosts) recognized as epidemiologically relevant (WHO, 2001a). Significant contributions to the epidemiological knowledge were made by studies on the dynamics of intermediate host populations and their relationships to landscape characters (Giraudoux et al., 2002).

### 3.1.2.3 Expansion or new detection of endemic areas?

By the end of the 1980s, *E. multilocularis* was known to occur in foxes in Central Europe only in four countries, including Austria, France, Germany and Switzerland (Stössel, 1989; Eckert, 1996). Further examinations of foxes (mostly large numbers) performed since 1989 revealed that the European endemic area of *E. multilocularis*, as determined by the presence of *E. multilocularis* in definitive hosts (predominantly foxes) is much larger than previously anticipated. By the mid-1990s, the known geographic range of *E. multilocularis* included the ‘endemic region in Central Europe, most of northern Eurasia, form Bulgaria and Turkey through most of Russia, and the newly independent nations of the former Soviet Union, extending eastward to several of the Japanese islands. In North America the cestode is found
throughout the northern tundra zone and in a discontinuous zone in the south’ (Schantz et al., 1995). How the image of the known endemic area in Europe has changed is evidenced by the fact that *E. multilocularis* has now been recorded in definitive hosts in at least 18 of the 28 member states of the European Union (status 2015, see Chapter “Epidemiology”).

Evidence of *E. multilocularis* spreading to previously nonendemic regions has been reported from Japan and North America. In Japan, the parasite was apparently introduced by means of foxes from the Kuriles to Rebun Island off the northern coast of Hokkaido where it was known to occur since 1936. In the period 1966 to 1971, infected humans and animals were found in the eastern part of Hokkaido, and in 1992 *E. multilocularis* was considered present throughout Hokkaido (Kamiya et al., 2004). In North America, the known endemic zone has extended from the northern tundra zone through parts of Canada further south to central states of the United States of America. It was assumed that arctic foxes migrating from the tundra southward were the means by which *E. multilocularis* became established in red foxes and rodents in Canada and subsequently in central North America (Rausch, 1967b, Rausch and Fay, 2002). However, recent studies suggest a more complex situation. For example, a European strain of *E. multilocularis* has been identified in Canada, which might have been introduced with foxes (for commercial use) or dogs imported from Europe (Massolo et al., 2014).

As mentioned above, in Europe, the known geographic range of *E. multilocularis* in foxes has extended considerably since the 1980s, and cases of human AE have been found in regions previously not recognized as endemic, for example in Poland and Lithuania. To explain this situation, various factors have been proposed, including *E. multilocularis* dispersal by means of fox migrations in recent years, increase of fox populations, changes of landscape characters, and increased disease awareness, misdiagnosis and underreporting of human AE cases, and the use inadequate techniques for diagnosing *E. multilocularis* in foxes and other definitive hosts. An excellent overview of this discussion is presented in review articles of Vuitton et al. (2003, 2015).

There is no doubt that by routine necropsy of foxes only with macroscopic inspection of the intestinal mucosa, infections with *E. multilocularis* can be easily overlooked, especially if worm numbers are low. This is supported by the fact that in Europe; the parasite has been detected in many regions soon after the employment of necropsy techniques targeted to *E. multilocularis*. Most likely, an increased disease awareness has also played a role in the identification of previously unknown endemic areas.
well-documented indicator for fox migrations since the end of the 1980s was the increasing fox numbers in cities in Europe, Canada and Japan (Deplazes et al., 2002) and the establishment of the life cycle including foxes and rodents in the urban environment (Deplazes et al., 2002, 2004).

Interesting and epidemiologically relevant questions are how long the recently detected endemic regions have existed unnoticed and when they might have been established. Knapp et al. (2009a) studied the genetic diversity of *E. multilocularis* in Europe using the microsatellite marker EmsB in association with matching the fox hosts geographical positions. A central core of the European focus was identified in Switzerland and the Swabian Jura (Germany) flanked by neighbouring regions where *E. multilocularis* exhibits a lower genetic diversity than that in the centre. The authors concluded that *E. multilocularis* has needed more than a few decades to migrate distances of more than 1000 km; ‘thus in those countries, the apparent emergence of human AE is more likely due to an active search as a consequence of disease awareness and only secondarily due to an increase of parasite prevalence’ (Knapp et al., 2009a).

### 3.1.2.4 Life cycle patterns of *Echinococcus granulosus* and *Echinococcus multilocularis*

In the past, at least 16 *Echinococcus* species were described (Verster, 1965; Ohbayashi, 1993), but subsequently only four of them were recognized as valid (*E. granulosus, E. multilocularis, Echinococcus oligarthrus, Echinococcus vogeli*) (Verster, 1965; Rausch, 1967a, Thompson, 1986a). The fact that 10 subspecies were morphologically recognized in *E. granulosus* and only three in *E. multilocularis* was an indication of a considerable intraspecific variation in *E. granulosus*. Studies of populations of *E. granulosus* recovered in different regions have demonstrated intraspecific variations in final and intermediate host assemblages as well as in morphological and other characteristics (Thompson, 1986a, 1995). Meanwhile intensive studies by various research groups have identified several strains of *E. granulosus* differing in their host preferences, infectivity to humans, and other characteristics, as described in detail in chapter *Biology and Systematics of Echinococcus* by Thompson, 2016. Less intraspecific variability has been described in *E. multilocularis*. Respective research in the last five to six decades has deeply changed and enriched the understanding of epidemiological interconnections and has an impact for disease prevention and control.
3.2 Clinical aspects and pathology

3.2.1 Echinococcosis in humans

The literature published at the turn of the 19th to 20th century is a rich source of information on clinical aspects and pathology of human echinococcosis. This may partially be due to the fact that autopsies of humans were formerly frequently performed, and some authors had collected and evaluated large numbers of cases. For example, in Munich/Germany, 14,830 autopsies were made in the period 1854 to 1887 (436 per year) (Schwarz, 1928), and Neisser (1877) listed in his thesis 968 echinococcosis cases, compiled from the literature and hospital reports, many of them with case histories. Albert Neisser (1855—1916) was born in Schweidnitz, Germany (now Swidnica, Poland) and studied medicine at the University of Breslau (now Wrocław), and in 1877 he published his dissertation on echinococcosis (‘Die Echinococcen-Krankheit’). In 1879 he discovered the causative agent of gonorrhoea (Neisseria gonorrhoeae) and was appointed to Professor of Dermatology at the University of Wrocław in 1907 (Figs 15 and 16).

At that time, clinical signs and pathologies of echinococcosis were quite well known, and CE and AE were distinguished as clinical entities although it was still uncertain whether these two forms of human echinococcosis are caused by a single or two different Echinococcus species. Neisser (1877), Langenbuch (1890) and Lehmann (1928) presented detailed descriptions of clinical signs and pathologies of CE, and Posselt (1928) contributed a comprehensive review of AE. The differences between both forms were clearly documented, and many of the previously known characteristic

Figure 15 A. Neisser (1855—1916). Wikipedia—die freie Enzyklopädie.
features are still valid (Ammann and Eckert, 1996; Pawlowski et al., 2001; Kern et al., 2004; Junghanss et al., 2008; Brunetti et al., 2010) (Fig. 17).

Over the years, clinical research and exchange of information has led to a better understanding of human echinococcosis, a more precise definition of clinical cases, and an international classification of disease entities. Such classification systems are relevant for improving the diagnosis and the prerequisites for therapeutic interventions. The WHO Informal Working Groups on Echinococcosis (IWGE) (see Section 5) developed an international classification of ultrasound images of abdominal CE (WHO-IWGE, 2003). This grading system allows clinicians to identify five different types of (liver) cysts (e.g., uni- or multilocular, active or inactive), to follow the development of cysts, to recommend specific procedures of intervention and to apply

Figure 16 Book of A. Neisser (1877): title page. Photo: J. Eckert.

Figure 17 Book of Langenbuch (1890): title page. Photo: J. Eckert.
standardized criteria in assessing the evolution of cysts after puncture—aspiration—re-aspiration (PAIR) or chemotherapy (WHO-IWGE, 2003; Junghanss et al., 2008). Sensitivity and specificity of ultrasound (US) examinations for abdominal cysts are high and reported to be at least 93% to 98% and 88% to 90%, respectively (Macpherson et al., 2003; WHO-IWGE, 2003). Based on the International Classification of Diseases and Related Health Problems (ICD 10), CE cases can be subclassified into several disease entities (Brunetti et al., 2010). The European Network for Concerted Surveillance of Alveolar Echinococcosis (see Section 5) and the WHO-IWGE have proposed a classification system for AE which includes imaging findings on the localization of the parasite in the liver, extrahepatic involvement of neighbouring organs, and absence or presence of distant metastases (PNMs) (Kern et al., 2006). As in CE, definition of AE cases follows the ICD system mentioned above (Brunetti et al., 2010). Regarding details and other clinical aspects, the reader is referred to the reviews of Junghanss et al. (2008) and Brunetti et al. (2010) and Chapter “Clinical management...”.

In the old literature, the tumour-like proliferation and metastasis formation of *E. multilocularis* metacestodes in the human body was well recognized, but the mechanisms were unknown (Posselt, 1928). The proliferation of the parasite was explained by Jahn (1927) with diverticule formation of the vesicle wall (germinal and laminated layer) resulting in a network of many interconnected vesicles of various diameters and forms. Rausch (1954) infected voles (*Microtus pennsylvanicus*) orally with *Echinococcus* eggs obtained from arctic foxes and studied the development of the alveolar metacestodes and the hosts’ histological reactions from 20 h to 170 days p.i. Metacestodes developed primarily in the liver; they grew rapidly and formed aggregates of cysts usually less than 10 mm in diameter. In long-lasting infections, metastatic foci were observed in various organs. At 14 days p.i., when a subgerminal ‘laminated layer’ was not yet discernable, Rausch observed ‘numerous isolated masses of germinal tissue which are the fore-runners of new vesicles.’ Regarding metastasis formation, Rausch (1954) thought that the dilatation of blood vessels in the liver resulting from larval growths ‘apparently is adequate to allow bits of larval tissue to pass into the hepatic vain and thence into the systemic circulation.’ According to Lukashenko (1975), parasite proliferation is due to internal fission of vesicles in two or more parts which form daughter vesicles after separation. Vogel (1978) reviewed the literature (back to Leuckart, 1886 and others) and discussed various hypotheses regarding the growth of *E. multilocularis* metacestodes. In his own studies with experimentally infected voles (*M. arvalis*), he
had identified by light microscopy small protuberances of the germinal layer, devoid of a central cavity and a laminated layer, that he regarded as ‘juvenile form of the vesicular stage- excellently suited to enter narrow inter spaces.’

Following Vogel’s studies, Eckert et al. (1983) observed that the subcutaneous transplantation of *E. multilocularis* metacestode tissue into the neck region of rodents (*Meriones unguiculatus*) resulted not only in parasite growth but also metastasis formation first in regional lymph nodes and subsequently in the lungs, indicating parasite spreading via the lymph and blood system. In further electron microscopical studies, slender solid cell columns (buds) protruding from the germinal layer were detected, that were devoid of a laminated layer. These root-like protrusions infiltrated the surrounding host tissue and transformed later into tube-like structures with a central cavity, covered by a laminated layer (Mehlhorn et al., 1983). Thus the previous observations of Rausch (1954) and Vogel (1978) could be confirmed and extended. To our knowledge, there are no reports on such structures in metacestode tissue obtained from humans. It can be assumed that proliferation involving the root-like protruberances only occurs in very young, actively proliferating parts of the metacestode. Tappe et al. (2010b) reconstructed three-dimensional images of histological sections of metacestode material from AE patients and observed a root-like network of interconnected tubules.

In the old literature, the immunological interplay between metacestodes of *E. granulosus* and *E. multilocularis* and their hosts was discussed in terms of the role of parasite antigens in stimulating humoral antibody and cellular skin reactions as well as anaphylactic events after sudden release of hydatid cyst fluid (Lehmann, 1928). Furthermore, the chemical composition of cyst fluid was discussed in some detail (Neisser, 1877). Recent developments of the immunobiology of the *Echinococcus* infection are described in previous reviews (e.g., Heath, 1995; Lightowlers and Gottstein, 1995; Gottstein and Hemphill, 2008; Mejri et al., 2010; Siracusano et al., 2012; Zhang et al., 2012) and in Chapter “Immunology...”.

### 3.2.2 Echinococcosis in animals

A vast older literature exists on CE in many intermediate and aberrant host species, including natural history of the cysts, their organ localization, clinical manifestations, prevalence in various countries and regions etc. (Dardel, 1927; Hosemann, 1928; Thompson and Allsopp, 1988; WHO, 2001a; see also databanks). Since the 1990s numerous reports on naturally acquired AE in a wide spectrum of mammalian accidental hosts have been published,
including nutria, wild boar, domestic pig, horse, dog and various genera of monkeys. Severe clinical implications and lethal cases of AE were observed in dogs and monkeys (reviewed in WHO, 2001a; Deplazes and Eckert, 2001). For information on AE infections in natural intermediate hosts and the wide spectrum of intermediate host species, see reviews (WHO, 2001a; Rausch, 1986, 1995, Vuitton et al., 2003).

3.3 Diagnosis of echinococcosis

3.3.1 Diagnosis in humans

Formerly, the clinical diagnosis of echinococcosis in humans was almost exclusively dependent on symptoms which could be discovered by inspection and palpation (e.g., distended abdomen, palpable fluctuating cysts) (Langenbuch, 1890; Lehmann, 1928). Although the clinical manifestations, caused by cysts of *E. granulosus* in various organ systems, were quite well known to authors in the second half of the 19th century, differential diagnosis (tumours, liver abscess etc.) was difficult in many cases. Therefore over the years, attempts were made to introduce and apply improved diagnostic methods.

3.3.1.1 Diagnostic puncture

Neisser (1877) underlined the importance of puncture as a diagnostic tool and presented a table with detailed information on the differential diagnosis of CE, ascites, ovarian cysts, hydronephrotic lesions etc., including data on specific weight and composition of the puncture fluid. Diagnostic puncture, which had already been occasionally applied in the ancient world and the middle ages, was widely used in the 19th and the beginning of the 20th century. This method was regarded as useful and mostly harmless, but the risks were also recognized (dissemination of protoscoleces, allergic reactions, bacterial infections etc.) (Langenbuch, 1890; Hosemann, 1928). According to Lehmann (1928), puncture was a malpractice and ‘prohibited in all circumstances.’ Still today, fine-needle puncture is used occasionally (e.g., cysts or unclear lesions in seronegative persons).

3.3.1.2 Immunodiagnosis

Immunodiagnosis of echinococcosis in humans dates from the beginning of the 20th century. For the detection of circulating anti-*Echinococcus* antibodies Ghedini, Weinberg and Parvu (Weinberg, 1909; Lehmann, 1928) developed a complement fixation test (also known as Ghedini–Weinberg test), and Fleig and Lisbonne (1907 in Lehmann, 1928) a precipitation test while Casoni and Botteri (in Lehmann, 1928) invented an intradermal
test (later known as Casoni test). From the 1950s, these tests were complemented or gradually replaced by better methods, such as indirect haemagglutination test, bentonite and latex agglutination tests, immunoprecipitation and immunoelectrophoresis. Some of these tests were quite sensitive in detecting CE, especially of the liver, but a general problem was the low degree of specificity (Kagan, 1968; Varela-Diaz and Coltorti, 1976; Rickard and Lightowlers, 1986). Later on, the repertoire of antibody tests was extended by further procedures, including the indirect fluorescent antibody test, the enzyme-linked immunosorbent assay (ELISA) and some secondary tests. The use of purified or recombinant antigens in modern testing procedures significantly improved the reliability of diagnostic results (Lightowlers and Gottstein, 1995; WHO, 2001a; further information see Chapters “Immunology...” and “Laboratory diagnosis”).

3.3.1.3 Imaging procedures

Around 1900 radiography was introduced as a new diagnostic technique, followed since the late 1960s by ultrasonography, computed tomography, angiography, cholangiography, magnetic resonance imaging, and in the early 1990s, by positron emission tomography. These imaging procedures presented new options for diagnosing of CE and AE in humans as documented in an overview by von Sinner and Lewall (2001). The introduction of US for the diagnosis of human abdominal echinococcosis in the early 1970s was of special relevance, not only for the clinical diagnosis as described above, but also for mass screening of populations (see below).

3.3.1.4 Mass screening of human populations

The use of portable ultrasound scanners for mass screening of populations since the mid-1980s and early 1990s was a great step forward. Community-based mass screenings for CE have been performed in several countries in Africa, South America and Asia (China), including remote areas and large groups of people (up to 20,220 in one of the studies) (Macpherson et al., 2003). In these studies, ultrasound mass screening has proven a reliable and relatively cheap method for demonstrating the true extent of human CE (Macpherson and Milner, 2003; Macpherson et al., 2003). Screening surveys for human AE have also been conducted in endemic areas, for example, in China and France (Craig et al., 1996). However, serological tests are required in many cases to confirm the aetiology of the lesions (Macpherson and Milner, 2003; Macpherson et al., 2003). In some of these programmes, ELISAs, in combination with western blot analyses, were used for detection of specific
serum antibodies. In view of the low prevalence of human AE in most of
the endemic areas, it is essential to use only test systems which are highly
sensitive and specific (reviewed in WHO, 2001a). The special value of
ultrasound mass screening is that cases of CE and AE can be detected in an
early stage thus improving the chances for effective treatment and a better
prognosis.

3.3.2 Diagnosis of echinococcosis in animals

3.3.2.1 Definitive hosts

In the past, the diagnosis of the intestinal *E. granulosus* infection in living dogs
was highly unreliable because the eggs of *Echinococcus* and *Taenia* species are
morphologically indistinguishable, and spontaneously and irregularly elimi-
nated small *Echinococcus* proglottids can easily be overlooked. Better results
were obtained by examination of faecal samples collected after purgation
of dogs with arecoline hydrobromide. This method was used as a diagnostic
aid in many of the control programmes and in epidemiological studies but
can now be replaced by the coproantigen ELISA (see below). The exami-
nation of the small intestine for mature or immature *E. granulosus* stages at
necropsy is restricted for obvious reasons to small numbers of dogs. The pur-
gation and necropsy techniques have been described and reviewed in various
publications, including WHO documents (WHO, 1984b, 2001a).

Necropsy was the only option for diagnosing intestinal *E. multilocularis* in
foxes and other definitive hosts. However, at routine necropsies with
macroscopic inspection of the mucosa, the parasites can be easily missed,
especially when worm numbers are low. Therefore since the late 1970s in
many studies, either the intestinal scraping technique (IST) or the sedimen-
tation and counting technique (SCT) was employed after the intestines or
carcasses had been kept deep frozen at ~80°C for at least 4 days (routinely
7 days for carcasses) in order to kill parasite eggs and to reduce or exclude a
potential infection risk for laboratory personnel (Eckert et al., 2001; Mathis
and Deplazes, 2004). The IST has been widely used in European epidemi-
ological studies on *E. multilocularis* in foxes, but it may underestimate the true
prevalence by about 20% (Mathis and Deplazes, 2004). The SCT (or mod-
ifications of it) has usually a higher sensitivity (over 90%) (Hofer et al., 2000;
Mathis and Deplazes, 2004). Both the IST and SCT are labour intensive and
cost intensive (Mathis and Deplazes, 2004).

In the 1990s, significant progress was achieved by the development of
methods for (1) detecting *Echinococcus*—specific antigens by ELISAs in faecal
samples (Allan et al., 1992; Deplazes et al., 1992; others reviewed in Allan and
Craig, 2006) or (2) DNA in faecal material or in isolated eggs (Bretagne et al., 1993; Mathis et al., 1996; Deplazes et al., 2003; Mathis and Deplazes, 2004, 2006; Trachsel et al., 2007) by molecular techniques. These methods detect intestinal infections with *Echinococcus* species with high sensitivity and specificity (reviewed in Allan and Craig, 2006; Mathis and Deplazes, 2004) and can be applied in vivo (faecal samples) and postmortem (intestinal content) examinations of animals. Furthermore, DNA detection allows the identification of *Echinococcus* species and strains (Stefanic et al., 2004) and the species-specific detection of *Echinococcus* eggs in the environment (faecal samples, soil) or in other materials (e.g., vegetables) (Mathis and Deplazes, 2004).

### 3.3.2.2 Intermediate and aberrant host animals

Early lesions caused by *Echinococcus* species in organs of animals are sometimes difficult to identify macroscopically or histologically. In such cases, DNA detection is a valuable diagnostic aid. Furthermore, serological examinations for specific antibodies have gained significance in the diagnosis of CE or AE in certain animals, such as monkeys or dogs.

### 3.4 Treatment of echinococcosis

#### 3.4.1 Treatment of human echinococcosis

**3.4.1.1 Cyst puncture**

As early as in ancient times and the middle ages, doctors had tried to inactivate hydatids by **puncture** or **minor surgery** (see above diagnosis). In the mid-19th century, the French physicians Récamier and Moissenet began to employ this method specifically for treatment of CE (Langenbuch, 1890). *Echinococcus* cysts were punctured with a cannula, and the fluid was aspirated with a syringe in order to harm the parasite. Cysts were also drained by means of a trochar (Langenbuch, 1890). After Boinet in France and Weber in New York had recommended in 1851 to inject tincture of iodine into punctured cysts, solutions of many other substances were used in this indication (usually after aspiration of some cyst fluid) with the intention of increasing the detrimental effects on hydatids. The list of substances (and natural fluids) is long and included ‘filix mas’ (‘worm fern,’ an anthelmintic, containing flicic acid), ox bile, chlorinated water, copper sulphate, β-naphthol, boric acid, salicylic acid, mercury (II) chloride (sublimate), alcohol, formalin (1%) and formalin—glycerin (Neisser, 1877; Langenbuch, 1890; Lehmann, 1928). According to Neisser (1877), of 160 patients with abdominal hydatids, 97 (61%) were cured after puncture (single or repeated), aspiration and injection (substances not defined). The risks of puncture
(spillage of hydatid fluid with subsequent dissemination of protoscoleces, anaphylactic shock, toxicity of the injected chemicals) were already well known in the 19th century. However, until recent years, formalin was injected into cysts for intraoperative killing of protoscoleces. In 1996 a WHO expert group deemed formalin unsafe and recommended that its use be stopped (WHO, 1996).

3.4.1.2 Puncture—aspiration— injection— reaspiration
The old principle of puncture experienced a revival within an improved and thoroughly controlled procedure, which was developed in the mid-1980s as the so-called PAIR method. PAIR includes the following steps: (1) percutaneous cyst puncture under ultrasonographic guidance, (2) aspiration of a substantial portion of cyst fluid, (3) injection of a parasitocidal solution (20% sodium chloride solution or preferably 95% ethanol; approximately an equivalent of one-third of the amount aspirated), and (4) reaspiration of the fluid content after 5 min in case of ethanol injection and at least 15 min if sodium chloride solution is used (Ben Amor et al., 1986; Filice and Brunetti, 1997; Brunetti et al., 2010). In 2001 the WHO Informal Working Group on Echinococcosis (WHO-IWGE, see below) published guidelines for the indication and use of PAIR as well as on its benefits and risks (WHO, 2001b; Brunetti et al., 2010). PAIR is considered a minimal invasive and alternative technique for surgery or chemotherapy of CE patients that harbour certain types of hepatic cysts defined according to an international classification system (WHO-IWGE, 2003). For further information on benefits and risk of PAIR, see Junghanss et al. (2008).

3.4.1.3 Surgery
Surgery has always played a prominent role in the therapy of echinococcosis. With regard to CE, Lehmann stated in 1928 ‘that treatment of the Echinococcus today is fundamentally purely surgical.’ Accordingly, detailed descriptions of different surgical techniques can be found in the older literature (e.g., Langenbuch, 1890; Lehmann, 1928) and in the following periods (e.g., Morris and Richards, 1992; Uchino et al., 1993) up to liver transplantation (Koch et al., 2003). The use of surgery for treatment of CE and AE as single (potentially curative) method or in combination with chemotherapy and adjuvant procedures, as well as indications and contraindications is discussed in several reviews prepared by groups of international experts (Pawlowski et al., 2001; Junghanss et al., 2008; Brunetti et al., 2010).
3.4.1.4 Chemotherapy

In the literature of the 19th and the early 20th century, many attempts of systemic chemotherapy of CE and AE are described, reviewed by Langenbuch (1890) and Posselt (1928). They included, for example, ‘heroic’ treatments with emetics which were intended to cause cyst rupture and draining of the fluid into a body cavity. Laxatives, concentrated sodium chloride solutions or potassium iodide, turpentine, kalium iodide, or mercury (I) chloride (calomel) and other substances were used for systemic treatment. Langenbuch (1890) mentioned that by calomel treatment, ‘man became more poisoned than the worm.’ Later approaches of chemotherapy with atoxyl, neosalvarsan, arsenobenzole and thymol compounds failed to show success (Thiodét, 1954/55, Burkhardt, 1981). Thymol injections were still used in the 1960s, but there was no sound evidence for their efficacy against CE or AE neither in patients nor in experimental animals (Burkhardt, 1981).

### 3.4.1.4.1 Chemotherapy with benzimidazoles

Until the mid-1970s, many attempts to find antiparasitic drugs against experimental larval echinococcosis in rodents were unsuccessful. The tide turned in 1974 after Thienpont et al. (1974), researchers at Janssen Pharmaceutica Beerse, Belgium, had detected the efficacy of mebendazole against metacestodes of *T. taeniaeformis* in mice. Scientists in Australia described a high efficacy of this drug against metacestodes of *T. pisiformis* in rabbits and of *Mesocestoides corti* and *E. granulosus* in mice (Heath and Chevis, 1974; Heath et al., 1975). Authors in Russia (Krotov et al., 1974) and the United States of America (Campbell et al., 1975) reported that the tumorous growth of *E. multilocularis* metacestodes in rodents can be inhibited by treatment with increased doses of mebendazole.

Further detailed experimental studies revealed that prolonged oral treatment of rodents with albendazole, fenbendazole, flubendazole and mebendazole significantly (mostly >90%) inhibited the proliferation of *E. multilocularis* metacestodes, damaged the parasite structure, prevented metastasis formation and prolonged the survival time of the treated animals, but usually did not kill the parasites. On the other hand, in the same model, cysts of *E. granulosus* could be killed (Eckert and Pohlenz, 1976; Eckert et al., 1978; Burkhardt, 1981; Schantz et al., 1982; Eckert, 1986). Concurrently,
pharmacological studies on the bioavailability of high oral doses of benzimidazoles and the presumably effective serum drug levels were performed in experimental animals and humans (Witassek et al., 1981; Luder et al., 1986). The results formed the basis for monitoring of serum drug levels in patients and adaptation of the oral doses.

Among the early reports on the use of high oral mebendazole doses against AE in humans were those of Akovbiantz et al. (1977) in Switzerland and Wilson et al. (1978) in Alaska, and against CE communications of Bekhti et al. (1977) in Belgium, Danis et al. (1977) in France, Beard et al. (1978) in Australia and Al-Moslih et al. (1978) in Iraq (for further references, see Schantz et al., 1982). In 1980 an international workshop on ‘Chemotherapy of Larval Echinococcosis in Animals and Humans’ was organized by the Janssen Foundation at Janssen Pharmaceutica, Beerse, Belgium, which was particularly supported by Dr Paul A. Janssen and his coworkers (Schantz et al., 1982). Since most of the early studies included only single or small numbers of patients and had given rather inconsistent results, the Swiss Study Group on Echinococcosis (steering committee members: A. Akovbiantz, R. Ammann, J. Bircher, J. Eckert) suggested that the WHO Parasitic Disease Programme (WHO/PDP) at WHO in Geneva coordinate international studies on the treatment of human echinococcosis with benzimidazoles (WHO/PDP, 1981). The project was supported by Dr A. Davis (Director, PDP), Dr Z. Matyas (Chief, Veterinary Public Health [VPH]) and Dr Z. Pawlowski (Senior Medical Officer, PDP) and launched in 1981, based on a uniform protocol (WHO/PDP, 1981, 1984). In 1986 the first results of a multicentric trial were published, which included 85 CE and 54 AE patients treated with mebendazole, albendazole or flubendazole at clinical centres in Anchorage, Beirut, Besançon, Paris, Rome, Sofia and Zurich. Pharmaceutical companies (Janssen Pharmaceutica, Smith, Kline & French) and several University institutes and hospitals cooperated in the studies (Davis et al., 1986). In the following years, various aspects of chemotherapy of human CE and AE were subjects of discussions at workshops or conferences and numerous publications (reviewed in Schantz et al., 1982; Eckert, 1986; Ammann and Eckert, 1995; Horton, 1997; WHO, 2001a; Horton, 2003; Eckert and Deplazes, 2004; Kern, 2004, 2006; Junghanss et al., 2008, and others). The continuous interest of WHO (Dr F.-X. Meslin, Dr T. Fujikura, Dr Z. Pawlowski, Dr L. Savioli) into echinococcosis and the international cooperation of research groups within the framework of ‘WHO Informal Working Groups on Echinococcosis’ (see below) proved to be stimulating and important for the further development of
chemotherapy. Methods and results were discussed and evaluated at several international meetings, for example, 1983 in Geneva, Switzerland (WHO, 1984a); 1990 in Anchorage, Alaska; 1992 in Besançon, France (WHO/CDS/VPH, 1992); 1993 in Beijing, China (WHO/VPH, 1993); 1994 in Al-Ain, United Arab Emirates (WHO, 1996) and 1995 in Hokkaido, Japan. In 1996 these efforts resulted in the publication of ‘Guidelines for treatment of cystic and alveolar echinococcosis in humans’ prepared by numerous experts of the WHO-IWGE (WHO, 1996). An updated guideline was published in 2010 (Brunetti et al., 2010). Results on the benefits and problems of chemotherapy of human CE and AE have been reviewed in various articles (e.g., Ammann et al., 1999; Pawlowski et al., 2001; Eckert and Deplazes, 2004; Kern, 2006, 2010; Eckert et al., 2011). Chapter “Clinical management...”.

### 3.4.1.4.2 Alveolar echinococcosis

Historically, AE had a high lethality rate in untreated patients of 90% within 10 years from the onset of clinical symptoms and virtually 100% within 15 years (Ammann and Eckert, 1996). In a Swiss study, the analysis of data of 329 patients over a period of 35 years revealed that current case management and treatments (improved diagnosis and surgery, chemotherapy with mebendazole or albendazole, and other measures) substantially improved the life expectancy of AE patients compared to the 1970s. Whereas the average life expectancy of a male AE patient in 1970 was 6.2 years, it increased to 25.1 years in 2005 (Torgerson et al., 2008). Vuitton (2009) concluded that ‘benzimidazoles have deeply modified the management of cystic echinococcosis patients and life expectancy of alveolar echinococcosis patients.’

Due to the activities and endurance of Rudolf Ammann (1926–2015), Professor of Gastroenterology at the University Hospital Zürich, and a group of colleagues and coworkers (see list of references), a large group of AE patients under treatment and medical care was observed in Switzerland over more than three decades (Ammann et al., 1999, 2004; Kadry et al., 2005; Torgerson et al., 2008). A sign of R. Ammann’s tireless passion for echinococcosis research is that the results of his last long-term study were published 3 months before his death (Ammann et al., 2015).

### 3.4.1.4.3 Cystic echinococcosis

Chemotherapy of CE patients with albendazole or mebendazole is often only partially effective, and rarely curative with complete regression of the cysts. Results for over 2000 well-controlled cases treated with benzimidazoles and evaluated for up to 12 months have shown that 10% to 30% of the cysts die (cure),
50% to 70% respond (degeneration or size reduction of cysts), and 20% to 30% do not exhibit morphological changes (Horton, 1997; Todorov et al., 1992; Pawlowski et al., 2001; Horton, 2003; Junghanss et al., 2008). Based on a meta-analysis, including 711 patients, it was estimated that even 2 years after initiation of treatment, 40% of the cysts are still active or become active again (Stojkovic et al., 2009).

Although chemotherapy of human AE and CE with benzimidazoles represents significant progress, these drugs are not fully satisfactory. In recent years, several substances have been tested in vitro or in laboratory rodents, but so far no drugs superior to benzimidazoles have been developed for use in humans (Hemphill et al., 2010).

### 3.4.2 Chemotherapy of intestinal Echinococcus infections in carnivores

One of the key measures to prevent CE in humans is mass treatment of dogs against *E. granulosus* (see below). Up to 1977, several anthelmintics were used in this way, including arecoline hydrobromide, bunamidine hydrochloride, niclosamide, and nitroscanate (Gemmell, 1978). Since arecoline hydrobromide acts as a purgative and often eliminates only a proportion of the *Echinoccus* burden, its value in control programmes and as a diagnostic tool (see above) is limited. The other anticestodal drugs mentioned above had certain limitations and were not fully satisfactory for various reasons. A significant advance was the introduction of praziquantel. Its efficacy against adult cestodes was announced in 1975 by Thomas et al., scientists of the Bayer Company, Germany. At a single dose, this well-tolerated drug has a very high and reliable efficacy against mature and immature intestinal stages of *Taenia* species as well as of *E. granulosus* and *E. multilocularis*. Since 1977 it has been successfully and widely used for treating individual dogs or cats infected with *Echinococcus* species and in control campaigns against *E. granulosus* in dogs and *E. multilocularis* in dogs and foxes (see below).

### 3.5 Control and Prevention

#### 3.5.1 Echinococcus granulosus

Shortly after the elucidation of the life cycle of *E. granulosus* in 1853, first proposals were made for controlling this parasite. For example,
Küchenmeister (1855) in Germany suggested official regulations that organs of slaughter animals containing ‘bladder worms’ should not be left for dogs to eat as food but should be destroyed. In view of the environmental contamination with Echinococcus eggs, he recommended caution with unboiled drinking water, raw root vegetables or fruit windfall and demanded from governments educational programmes on echinococcosis. In Iceland, which had previously a high incidence of human CE, Dr Arthur Leared, an English physician who visited the country in 1862, recommended the destruction of hydatid cysts and the treatment of dogs with anthelmintics (Grove, 1990; Thakur, 2002).

The first long-term control campaign was started in Iceland in 1864 with an educational programme introduced by Harald Krabbe (1831–1917), then assistant at the Royal and Agricultural College in Copenhagen, Denmark (Enigk, 1986). The first legislation to control hydatid disease in Iceland was established in 1869, including registration of all dogs, payment of tax on nonworking dogs, destruction of hydatid cysts and infected viscera and several other measures, such as restrictions to dog populations, and annual treatment of dogs, initially with areca nut (containing arecoline as an active ingredient), from 1930 with arecoline hydrobromide, and from 1977 with praziquantel (Beard, 1973; Thakur, 2002; PAHO, 2002). The programme lasted 110 years from 1869 to 1979. Iceland is now free of E. granulosus; the last human case of CE was diagnosed in 1960.

Since 1959, further long-term and large-scale (nation-wide or regional) control campaigns have been performed, including those in New Zealand (1959–97) (Gemmell, 1978, 1987, 1990; Heath et al., 2002), Tasmania (Meldrum and McConnell, 1968; Thompson, 2002), Falkland Islands (1965–77) (PAHO, 2002), and Cyprus (1971–94) (Polydorou, 1984, 1994; Economides and Christofi, 2002; Christofi, 2011). These programmes were based on general measures outlined by Atwater (1969) in the textbook ‘Veterinary Medicine and Human Health,’ edited by Calvin W. Schwabe (1927–2006), Professor of Epidemiology at the School of Veterinary Medicine and School of Medicine, University of California, Davis, United States of America (Schwabe, 1969). He was widely known as the father of veterinary epidemiology and directed as a consultant the WHO global hydatid research and control programme in 1960 (Kass et al., 2006). Specific plans and strategies for the control of E. granulosus were substantially
elaborated by M.A. Gemmell and his team in New Zealand, summarized by Atwater (1969) and in WHO guidelines (WHO, 1981, 1984b). Essential components of these programs were legislation, the establishment of a control authority, long-term funding, collection of base-line data (human cases of CE, infection rates of dogs and intermediate hosts), collection and evaluation of continuing data, educational measures and technical control measures. These programs employed several key control measures, such as sanitary education, surveillance of food animals, construction and improvement of slaughterhouses, meat inspection, adequate disposal of slaughter offal, quarantine of premises with infected dogs and livestock, registration of dogs, demonstration of the infection in dogs, and dog dosing with anticestodal drugs at regular intervals (e.g., four to eight times a year with praziquantel). The programme in Cyprus included a strong policy on killing of infected ownerless and owned dogs (PAHO, 2002).

The structures and results of these programs were reviewed on several occasions, for example, up to 1974 by the Pan American Zoonoses Center and WHO (Gemmell and Varela-Diaz, 1980), by PAHO in 1994 and 1999 (PAHO, 1994, 2002), and later by Craig and Larrieu (2006) and WHO-IGWE (2011). Furthermore, related data are documented in many publications (e.g., Gemmell and Lawson, 1986; Gemmell, 1987; Schantz et al., 1995; WHO, 2001a). Over many years, these programs resulted in a significant reduction of the infection rates of dogs, sheep or other livestock and humans. Until 1999 the programs in New Zealand, Tasmania and the Falkland Islands had achieved the consolidation or maintenance of eradication phase (PAHO, 2002). In Cyprus, eradication was claimed in 1985, but control had to be reintroduced in 1994 (PAHO, 2002) and appeared to be successful (the last infected dog and intermediate hosts were found in 1996 and 2010, respectively) (Christofi, 2011). Since the 1970s, several South American countries have initiated control programs, including regions in Argentina, Uruguay, Brazil, Chile and Peru (Gemmell and Lawson, 1986; PAHO, 1994). The programs in Argentina and Chile were restricted to small parts of the endemic areas and are classified as partially successful; others have been discontinued or modified from the original design (Gavidia, 2011). Control programs have also been initiated in other regions, for example, more recently in Kyrgyzstan (Abdykerimov, 2011) and China (Wang, 2011). In China, control programmes were implemented in 2006
in 10 counties in the Sichuan Province and extended in 2010 to 170 counties in seven provinces or regions (Sichuan, Xinjiang, Inner Mongolia, Gansu, Qinghai, Ningxia, and Tibet) (Wang, 2011). In Sichuan Province, the proportion of diagnosed CE patients dropped from 2.4% (4247/178,358) in 2008 to 0.3% (717/237,399) in 2010, and the rates of coproantigen-positive dogs in the same period from 18% to 15.9% (Wang, 2011).

The successful historical examples show that control campaigns against *E. granulosus* are long-term actions which require a high expenditure of time and financial resources. Therefore in recent programmes, efforts are made to introduce innovations and improvements, such as mass population screening (ultrasound examinations, serology) and treatment of human CE cases in order to increase the awareness and health status of local people, and vaccination of livestock with the new EG95 vaccine (Heath et al., 2003; Craig, 2011; Lightowlers, 2006, 2011; Torgerson, 2011; Wang, 2011). Mathematical models are useful for estimating the disease burden for the community and for evaluating various control options (Torgerson, 2003, 2006).

### 3.5.2 Echinococcus multilocularis

Control of *E. multilocularis* is very difficult because the primary cycle is sylvatic, typically with foxes as definitive and rodents as intermediate hosts. Rausch et al. (1990) performed a 10-year field trial in an Alaskan village where dogs in a synanthropic cycle had access to rodents as intermediate hosts. All dogs of the village were treated monthly with praziquantel (5 mg/kg body weight). By this intervention, the infection prevalence in rodents was reduced from 29% to 5%, but the infection rate rebounded quickly toward pretreatment levels when treatment was discontinued (Wilson, cit. in Schantz et al., 1995). In two large field trials in Germany, comprising areas of 3400 to 5000 km², the prevalence of *E. multilocularis* in sylvatic cycles could be significantly reduced (15%/67% and 3%/26%, respectively) by regular delivery of praziquantel-containing baits to foxes (Romig et al., 1999; Hansen et al., 2003; Romig, 2011). However, the prevalence rebounded to precontrol levels after termination of baiting (Romig, 2011). A significant reduction of the *E. multilocularis* prevalence in wild foxes by baiting with praziquantel was also documented in Hokkaido, Japan (Ito et al., 2003; Takahashi et al., 2013). On the other
hand, it has been shown that fox baiting in small (~1 km²), highly endemic urban areas can contribute to the reduction of environmental contamination with *E. multilocularis* eggs (Hegglin et al., 2003). However, the currently available data suggest that sustainable effects can only be achieved by permanent intervention schemes. In order to reduce the potential infection risk for pet owners, regular praziquantel treatment of dogs and cats which catch wild rodents is recommended in endemic areas.

### 3.6 Aspects of basic research

In his famous textbook on parasites of humans, Leuckart (1863) has described with impressive precision the anatomy and development of cestodes, including juvenile and adult stages of *‘Taenia echinococcus’* and the development of hydatid cysts with formation of brood capsules and proglottis. Subsequent generations of authors have referred to this basic information (e.g., Hosemann, 1928). Further studies on the structure, biology and physiology of *E. granulosus* and other species were performed later, increasingly since the 1950s, and have been reviewed by Smyth (1964), Thompson (1986b), McManus and Bryant (1986), Thompson (1995), McManus and Bryant (1995) and others.

#### 3.6.1 *Echinococcus granulosus*

Professor James Desmond Smyth (1917–99) was one of the eminent pioneers in the field of basic echinococcosis research. He was born in Dublin and obtained the degrees of BA and BSc in 1940 at the University of Dublin. Important positions in his career were Professor of Experimental Biology at Trinity College in Dublin (1955), Foundation Professor of Zoology in the School of General Studies at the National University, Canberra/Australia (1959–70) and Professor of Parasitology at Imperial College of Science and Technology, London (1970–82) (Bryant and Barwick, 2016). His major contributions to research on echinococcosis include the establishment of systems for the in vitro cultivation of *E. granulosus*, basic studies on the development of the adult parasite (germinat and somatic differentiation, proglottisation, segmentation etc.) and elucidation of external factors influencing parasite development (Smyth, 1964). Considerable progress has been achieved by the axenic cultivation of *E. granulosus* (sheep strain) with the reproducible development of proglottides to segmented, sexual mature stages without egg production. Furthermore, development of eggs or proglottides to sterile cysts was achieved (Smyth and Davies, 1974; Howell,
1986; Howell and Smyth, 1995). Of special interest were Smyth’s studies and considerations on the anatomical, biochemical and physiological host factors which might be involved in the parasite’s host and intermediate host specificity (Smyth, 1968). Smyth (1964) stated that speciation of *Echinococcus* is a complex matter, and he pointed to the possibility that different ‘races,’ ‘strains’ or ‘subspecies’ may exist (see chapter Biology and Systematics of *Echinococcus* by Thompson, 2016). Instructive and innovative presentations of the biochemical—physiological and immunological parasite—host interactions were characteristic of his excellent text books (Smyth, 1962). Smyth’s contributions provided an important basis for subsequent studies on host specificity, establishment of the parasites in the definitive host, activities of *Echinococcus* parasites at the intestinal interface etc. (Thompson, 1986b, 1995; Thompson and Lymbery, 2013) (Fig. 18).

### 3.6.2 Echinococcus multilocularis

In contrast to *E. granulosus*, in vitro cultivation of intestinal stages of *E. multilocularis* resulted in highly variable results (reviewed by Howell, 1986; Howell and Smyth, 1995). However, uniform development of pro-toscolecies to immature stages in vitro could be obtained (Thompson et al., 1990) as well as gravid worms following partial development in the definitive host (Thompson and Eckert, 1982). Rausch and Jentoft (1957) were apparently the first who reported the development of small vesicles of *E. multilocularis* from minced metacestode tissue (isolated from rodents) in complex media in vitro. They believed that the maintenance of larval
tissue in vitro may permit metabolic and other studies ‘hitherto not practicable.’ A significant step in this direction was the maintenance of *E. multilocularis* metacestode tissue blocks (0.1 to 0.3 g wet weight) in vitro with Eagle’s minimal essential medium with 10% foetal bovine serum and antibiotics (Ramp and Eckert, 1986, 1987). Various isolates retained the proliferative capacity in the intermediate host for up to 40 weeks. This system was further developed for long-term in vitro production of large numbers of vesicles (Hemphill and Gottstein, 1995), which can be used for in vitro drug screening and other purposes (Siles-Lucas and Hemphill, 2002). From such vesicles, primary *Echinococcus* cells that are devoid of host cells could be isolated and perpetuated in vitro (Spiliotis and Brehm, 2008; Brehm and Spiliotis, 2008). These achievements contributed to the reduction of experimental animals otherwise needed for strain maintenance in the laboratory. This applies also for cryopreservation of *E. multilocularis* tissue blocks which can be preserved in a viable stage in liquid nitrogen for many years (Eckert and Ramp, 1985).

Little exact information existed on the development of *E. multilocularis* in definitive hosts. Vogel (1957) infected experimentally 10 dogs, 4 red foxes and 6 cats with *E. multilocularis* with metacestode material from rodents or of human origin and obtained highly variable numbers of adult intestinal stages in all dogs and foxes and in 5 of the cats. However, a quantitative evaluation could not be done. Such studies were performed by Kapel et al. (2006) who infected red foxes, raccoon dogs, domestic dogs and domestic cats and determined the susceptibility and reproductive potential of these species. Furthermore, a detailed study of the development of the parasites in the various hosts was done (Thompson et al., 2006).

### 4. NEOTROPICAL *ECHINOCOCCUS* SPECIES

#### 4.1 Taxonomy

Several *Echinococcus* species, including *E. granulosus* s.l., *E. oligarthrus* and *E. vogeli*, occur in the neotropical region of Central and South America. It is assumed that *E. granulosus* was introduced with animals from Europe at the beginning of the 16th century (D’Alessandro and Rausch, 2008). For a long time, this species was considered to be the sole cause of echinococcosis in South America, although further *Echinococcus* species were known to occur in animals originating from this region (D’Alessandro et al., 1979), namely *E. oligarthrus* (Lühe, 1910) and *E. cruzi* (Brumpt and Joyeux,
In the 1960s the work of Lothar Szidat (1892–1973) stimulated new interest in this field as he had described three new species, namely *Echinococcus patagonicus*, *Echinococcus pampeanus* and *Echinococcus cepanzoi* (Szidat, 1971). Of these, *E. patagonicus* and *E. cepanzoi* were considered conspecific with *E. granulosus* (Schantz et al., 1975, 1976) and *E. cruzi* with *E. oligarthrus* (Verster, 1965; Rausch et al., 1984); *E. pampeanus* is most similar to *E. oligarthrus* (Rausch and Bernstein, 1972). After the description of *E. vogeli* by Rausch and Bernstein (1972), this species, together with *E. granulosus*, *E. multilocularis* and *E. oligarthrus*, was accepted as valid species (Rausch and Bernstein, 1972; Thompson, 1986b). In recent years, six genotypes of the *E. granulosus* complex have been identified in South American countries and were allocated to the newly established species *E. granulosus* s.s., *Echinococcus ortleppi*, and *Echinococcus canadensis* (Cucher et al., 2015; see also chapter Biology and Systematics of *Echinococcus* by Thompson, 2016). *E. granulosus* s.l. is not further considered in this section.

*E. oligarthrus* and *E. vogeli* are considered to be indigenous to South America and of ancient origin because their metacestodes typically occur in terrestrial rodents belonging to the group of Hystricognathi (e.g., pacas, agoutis). Such rodents were dominant in South America from ~22 to 5 million years before present (D’Alessandro and Rausch, 2008). Both species have a peculiar history. Johann Natterer (1781–1843), an Austrian scientist had collected helminths from a puma [*Felis (= Puma) concolor*] in Brazil and brought the material back to Vienna in 1836 (Tappe et al., 2008). Karl Moritz Diesing (1800–67), from 1827 custos at the ’Hofmuseum’ in Vienna, classified small cestodes from the puma initially as *Taenia crassicollis* and later as *Taenia oligarthra*. Maximilian F.L. Lühe (1870–1916), from 1909 Professor at the University of Königsberg (now Kaliningrad) (Enigk, 1986) studied Natter’s material and concluded that *T. echinococcus* and *T. oligarthra* are closely related (Lühe, 1910). Finally, Thomas W.M. Cameron (1894–1980), London School of Hygiene and Tropical Medicine, discovered the adult tapeworm in a jaguarundi (*Felis yagouaroundi*) (which had died in the London Zoo) and described it in detail as *E. oligarthrus* (Cameron, 1926). The story of the other indigenous species is also linked to a zoo animal as it was isolated in 1970 by Rausch and Bernstein (1972) from a bush dog (*Speothos venaticus*) captured in Ecuador and kept in the Los Angeles Zoo. This parasite differed from other *Echinococcus* species and was described as new species, *E. vogeli*, in ‘recognition of the contributions to the understanding of the taxonomy of *Echinococcus* species made by Professor Hans Vogel…’ (see p. 13 (refers to uncorrected proof)) (Rausch and Bernstein, 1972).
4.2 Life cycles and epidemiology

The natural definitive host of *E. vogeli* is the bush dog from which this species was isolated for the first time by Rausch and Bernstein (1972). Adult cestodes have also been found in a naturally infected domestic dog (D’Alessandro et al., 1981) and in experimentally infected dogs (see below). Pacas (*Cuniculus paca*) and agoutis (*Dasyprocta* spp.) are the only known natural intermediate hosts. Natural metacestode infections occur also in aberrant hosts, such as humans and monkeys (in zoos) and are known as polycystic echinococcosis (Rausch and D’Alessandro, 2002; D’Alessandro and Rausch, 2008).

The life cycle of *E. vogeli* was elucidated in 1955 by G.E. Vogelsang and J. Barnola in Venezuela and in 1975 by AD’Alessandro in Columbia, who infected dogs experimentally with cysts from an agouti (*Dasyprocta agouti*) and a paca (*C. paca*), respectively, and obtained strobilar stages of this species (Rausch et al., 1978). In further studies, Rausch et al. (1978) had reared strobilar stages of *E. vogeli* by infecting dogs with metacestodes isolated from human patients, naturally infected pacas and an agouti.

In the life cycle of *E. oligarthrus*, wild felids (puma, jaguar, jaguarundi etc.) act as definitive hosts and rodents (agoutis, pacas, opossums etc.) as intermediate hosts. The strobilar stage develops to maturity in experimentally infected domestic cats, and several rodent species are susceptible to experimental metacestode infections (Sousa and Thatcher, 1969; Rausch and D’Alessandro, 2002). In humans, the metacestode stages cause the unicystic form of echinococcosis.

After the description of the strobilar stage of *E. oligarthrus*, the metacestode stage remained unknown for a long time, although in 1914, the French parasitologists, Brumpt (1877–1951) and Joyeux (1881–1966), had found multilocular metacestodes in agoutis in Brazil which they tentatively named *E. cruzi*, but they also considered an association with *T. oligarthra* (Brumpt and Joyeux, 1924; Tappe et al., 2008). Many years later, Thatcher and Sousa (1968) studied a multilocular metacestode stage obtained from a nutria (*Myocastor coypus*) born in a United States Zoo. This stage was previously identified as *E. granulosus*, but Thatcher expressed the view that the nutria could be a natural host of *E. oligarthrus*.

A reliable diagnosis of the larval stages of *E. vogeli* and *E. oligarthrus* was difficult until Rausch et al. (1978) demonstrated that the dimensions of rostellar hooks of protoscoleces provide a means for the discrimination. Today, molecular methods allow a species-specific differential diagnosis (Tappe et al., 2008).
4.3 Human cases and pathology
The first cases of ‘alveolar hydatid disease’ were recorded in 1903 and in following years in Argentina by Viñas (in Rausch et al., 1978; D’Alessandro et al., 1995; Tappe et al., 2008), but it remained unclear for a long time, whether such cases are caused by atypical metacestodes of E. granulosus or other Echinococcus species (Rausch et al., 1978). Finally, at the end of the 1970s, studies by Rausch, D’Alessandro and coworkers (reviewed in Rausch and D’Alessandro, 2002; D’Alessandro and Rausch, 2008) demonstrated that the metacestodes developing in humans were predominantly that of E. vogeli. By Mar. 2007, in 12 Latin American countries, 172 human cases of neotropical echinococcosis had been recorded (D’Alessandro and Rausch 2008), and at least eight further cases were reported thereafter (Siqueira et al., 2007, 2010; Knapp et al., 2009b). Most of the cases were caused by E. vogeli (for details see reviews by Rausch and D’Alessandro, 2002; D’Alessandro and Rausch, 2008).

Of special interest regarding the pathogenicity of E. vogeli and E. oligarthrus in natural intermediate hosts and in humans are differences in structure and proliferation of the metacestode stages, as described by Rausch et al., 1981, Rausch and Alessandro 1999). Further information on this aspect, on clinical characteristics, diagnosis, epidemiology etc. can be found in excellent reviews of Rausch and D’Alessandro (2002) and D’Alessandro and Rausch (2008). These scientists deserve special recognition for their great contributions to the research into neotropical echinococcosis. Robert Rausch made most of his contributions when he was Professor at the University of Washington, Seattle, Washington (see also p. xx). AD’Alessandro was a member of Tulane University, New Orleans, Louisiana, and its Center for Medical Research in Cali, Columbia.

5. THE ROLE OF ASSOCIATIONS, INTERNATIONAL ORGANIZATIONS, AND INTERNATIONAL WORKING GROUPS IN ECHINOCOCCOSIS RESEARCH AND CONTROL
International associations and organizations have played and still play a significant role in the field of echinococcosis by facilitating international exchange of knowledge and promoting cooperation in research and control programmes. In 1941 the ‘Asociación International de Hidatilología’ was founded in South America, later known as ‘International Association of Hydatidiology (IAH)’ and since 2015 as ‘World Association of
Echinococcosis’ (WAE). Since its foundation this association has organized regular scientific meetings (‘Jornadas Internationales’), predominantly in South American countries, and international congresses in various countries around the world. In 1991 the 50th anniversary of the IAH was celebrated with a special congress in Rome. Congress abstracts or other communications were published in ‘Archivos Internationales de Hidatidosis.’ More information on the WAE can be obtained from http://www.echinoworld.org.

As early as 1948, the Pan American Health Organization (PAHO) and the World Health Organization (WHO) had published a resolution—based on a proposal submitted by representatives of Argentina, Brazil, Paraguay and Uruguay—recommending to the public health authorities of the American countries that they intensify the epidemiological investigation of hydatidosis and issue laws and regulations directed toward prevention and control of hydatidosis (PAHO, 1948). In 1978 the 31st WHO World Health Assembly recognized the need for elaboration of strategies and methods for the control of zoonoses and food-borne diseases and adopted a resolution on ‘Prevention and control of zoonoses and foodborne disease due to animal products’ (WHO, 1978). With reference to this resolution, ‘Guidelines for surveillance, prevention and control of echinococcosis/hydatidosis’ were prepared in cooperation between FAO/UNEP/WHO7 and published in two editions (WHO, 1981, 1984b), followed in 2001 by a ‘WHO/OIE8 Manual on echinococcosis in humans and animals: a public health problem of global concern’ (WHO, 2001a). These documents were prepared by large groups of international experts. WHO has developed a worldwide network of zoonoses centres in order to ‘provide essential technical cooperation to country health programmes with respect to zoonoses and related foodborne diseases’ (WHO, 1984b). Some of these centres are specifically concerned with echinococcosis, for example, in France (Université de Franche-Comté, Besançon), Italy (University of Pavia) and China (Xinjiang Medical University first Affiliated Hospital, and Xinjiang Center for Control and Prevention, Urumqi). Some activities of WHO and related organizations are mentioned in sections above, others are documented in various publications of which only some are included here as examples (Varela-Diaz and Coltorti, 1976; Gemmell and Varela-Diaz, 1980; PAHO, 1994; PAHO, 2002; WHO-IGWE, 2011). In 2013 the 66th WHO World Health

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Assembly adopted a resolution (WHA66.12) which calls member states to improve the health and social well-being of affected populations. Based on this resolution, a list of ‘neglected tropical diseases’ was published which also contains echinococcosis, although this disease is not restricted to the tropics (WHO, 2013).

Based on a proposal by Dr K. Bögel (then chief of the Veterinary Public Health Unit (VPH), WHO), ‘WHO Informal Working Groups on Echinococcosis’ (WHO-IWGE) were conceived in 1985 and officially established in 1987 with the intention to promote international exchange of knowledge and cooperation between groups working in various fields of echinococcosis (Meslin and Vuitton, 2011). The IWGE consisted of a coordinating group (chairman J. Eckert, University of Zürich, Switzerland, 1987 to 1995, vice-chairmen Lord E.J.L. Soulsby, University of Cambridge, United Kingdom and P.M. Schantz, Centres for Disease Control, Atlanta, United States of America) and the following subgroups: (1) Biology and strain variation (chairman R.C.A. Thompson, Murdoch University, Murdoch, Western Australia); (2) Immunology (M.D. Rickard, University of Melbourne, Werribee, Australia); (3) Immunodiagnosis (B. Gottstein, University of Berne, Switzerland); (4) Medical aspects (Z.S. Pawlowski, Clinic of Parasitic and Tropical Diseases, Poznań, Poland; (5) Epidemiology and Control (chairman: M.A. Gemmell, Hydatid Research Unit, Dunedin, New Zealand); and (6) Chemotherapy (chairman J. Eckert, Zürich). Each of the subgroups had invited several international experts for cooperation.

In 1995, Dr F.-X. Meslin (WHO/VPH) decided to transform all subgroups to a single group and to designate a coordinator for a 4-year term (Vuitton, 1997; Meslin and Vuitton, 2011). These were D.A. Vuitton (University Hospital Besançon, France, 1995 to 1999), P. Schantz (Centers for Disease Control, Atlanta, United States of America, 2000 to 2004), Ph. Craig (University of Salford, Manchester, United Kingdom, 2005 to 2010) and P. Kern (Department of Internal Medicine, University of Ulm, Germany, 2011 to 2015) (Meslin and Vuitton, 2011). Under the umbrella of this working group, a number of sections for special topics and tasks were established.

The WHO-IWGE held many expert meetings (for example9, in Montreal, Canada, 1987; Zürich and Geneva, Switzerland, 1988; East-Berlin, former German Democratic Republic, 1989; Stuttgart-Hohenheim,

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Germany, 1989; Besançon, France, 1992; Beijing, China, 1993; Al-Ain, United Arab Emirates, 1994; Geneva, Switzerland, 2011); they organized sessions on specific research topics at each World Congress of Hydatidology from 1990 to 2015 and published guidelines on treatment of CE and AE (WHO, 1996), PAIR (WHO, 2001b), PNM classification of alveolar echinococcosis (Kern et al., 2006), a consensus paper on the diagnosis and treatment of CE and AE in humans (Brunetti et al., 2010) and a WHO/OIE manual on echinococcosis in humans and animals (WHO, 2001a) (Figs 19 and 20).

Another example of international cooperation in the field of echinococcosis is the ‘European Network for Concerted Surveillance of Alveolar Echinococcosis,’ established in 1998 with the aims: (1) to determine the prevalence of human cases and identify risk factors as well as prognostic

Figure 19  Meeting of the WHO Informal Meeting of Working Groups on Echinococcosis Research, 13-16.09.1988, World Health Organization, Geneva. From left: first row: Mrs Fujikura (Japan), D. Heath (New Zealand), P. Schantz (United States of America), M. Rickard (Australia), C. Macpherson (United Kingdom), T. Fujikura (Japan, WHO Geneva); second row: Jiang Cipeng (China), E.J.L. Soulsby (United Kingdom), M. Gemmell (New Zealand), C. Arme (United Kingdom), B. Gottstein (Switzerland), N.N. partially hidden (Poland, WHO Geneva), M. Lightowlers (Australia), A. Thompson (Australia). Further group member J. Eckert (Switzerland, photographer). Original: J. Eckert. The authors regret that one person (N.N.) could not be identified.
factors and (2) to determine the role of final hosts (foxes, dogs and cats) as possible sources of infection for humans. This network—funded by the European Commission and other sources—was coordinated by D.A. Vuitton (University of Franche-Comté, Besançon, France) and P. Kern (Ulm University, Ulm, Germany) for human epidemiology (‘EurEchinoReg’), and by P. Giraudoux (University of Franche-Comté, Besançon, France) and T. Romig (University of Hohenheim, Germany) for animal epidemiology (‘EchinoRisk’). It stimulated the establishment of national reference centres and concerted data collection on human cases of AE (Kern et al., 2003; Tamarozzi et al., 2015). The network on human epidemiology has been reactivated in 2014 to 2015 to set up a fully integrated European Alveolar Echinococcosis Database ‘EurEchino’ in order to collect AE cases online all over Europe (Charbonnier et al., 2014). In parallel, the EC-funded

Figure 20 Meeting of the WHO Informal Working Group on Echinococcosis in Al-Ain, United Arab Emirates (UAE) October 1994. From left: first row: M. Kamiya, partially hidden (Japan); Vice Dean, Medical Faculty, Al-Ain (UAE); J. Eckert (Switzerland, chairman); local secretary of the meeting; D.A. Vuitton (France); J. Pawlowska (Poland); Y. Kamiya (Japan); A. McLeodham (Dean Medical Faculty, Al-Ain, UAE); F.K. Dar (Medical Faculty, Al Ain, vice-chairman). Second/third row: N.N partially hidden; N.N.; N.N.; G. N. Alwar (Lebanon); T. Todorov (Bulgaria); N.N.; P. Kern (Germany); Z. Pawlowski (Poland, vice-chairman); N.N.; H. Wen (China); N.N.; C.E. Tanner (Canada); L. Savioli (WHO, Geneva); P. S. Craig (United Kingdom); J. Horton (United Kingdom); N.N.; De Rycke (Belgium); W.N. von Sinner (Saudi Arabia). The authors regret that not all persons (N.N.) could be identified. Congress photo, collection J. Eckert.
project ‘Heracles,’ an international endeavour to coordinate studies on CE in Europe and Turkey, was established in 2013, coordinated by A. Casulli (Istituto Superiore di Sanità, Rome, Italy); it also includes an epidemiological collection of CE cases all over Europe (http://www.heracles-fp7.eu/erce.html).

After the major endemic area for CE and AE was disclosed in Western China at the end of the 1980s, internationally supported projects were launched, thanks to the European Commission then to the National Institutes of Health/National Sciences Foundation of the United States of America (TransTech projects, coordinated by P.S. Craig, Salford University and P. Giraudoux, Université de Franche-Comté, Besançon, France, and locally supported by Xinjiang University, Lanzhou Medical University, Sichuan Center for Control and Prevention, and Ningxia University, People’s Republic of China). These projects were the basis for the Chinese National Survey of Echinococcosis in the 2000s and the Chinese National Echinococcosis Control Programme launched by the People’s Republic of China in 2010 (Chinese Ministry of Health, 2007).

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