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Invited Review

Echinococcus as a model system: biology and epidemiology

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ABSTRACT

The introduction of *Echinococcus* to Australia over 200 years ago and its establishment in sheep rearing areas of the country inflicted a serious medical and economic burden on the country. This resulted in an investment in both basic and applied research aimed at learning more about the biology and life cycle of *Echinococcus*. This research served to illustrate the uniqueness of the parasite in terms of developmental biology and ecology, and the value of *Echinococcus* as a model system in a broad range of research, from fundamental biology to theoretical control systems. These studies formed the foundation for an international, diverse and ongoing research effort on the hydatid organisms encompassing stem cell biology, gene regulation, strain variation, wildlife diseases and models of transmission dynamics. We describe the development, nature and diversity of this research, and how it was initiated in Australia but subsequently has stimulated much international and collaborative research on *Echinococcus*.

1. Introduction

Echinococcus remains a major cause of zoonotic diseases of public health and economic significance (Jenkins et al., 2005b; Budke et al., 2006; Davidson et al., 2012; Hegglin and Deplazes, 2013). Despite advances in control strategies, clinical management and vaccine development, the parasite continues to thrive in countries throughout the world.

Hydatid disease, cystic and alveolar, is a typical cyclozoonosis that can be perpetuated in nature in wild animal cycles without impacting on public health but with human interference (Thompson, 2013), directly or accidentally, with spillover to domestic cycles can lead to severe clinical disease and death. It is also an important cause of economic losses to livestock industries, particularly *Echinococcus granulosus* in sheep and cattle (Table 1).

It is now well known that *Echinococcus* has a two-host life cycle with a sexual stage in the intestine of a carnivore definitive host and a unique, cystic larval stage in the tissues of non-carnivorous mammals and omnivores (Thompson, 1995). It is interesting that much of the research that revealed the unique features of the parasite's way of life were undertaken in Australia. This is not a coincidence and relates to the impact *Echinococcus* had on a developing agricultural society following early European settlement of a continent with huge temperate areas perfect to exploit for raising livestock.

It was the upsurge in sheep farming at the end of the 19th century, with expanding exports to Europe, that contributed to the serious and largely undocumented human health problem that existed during the late 19th and early 20th centuries (Gemmell, 1990). During the first half of the 20th century, there was a high incidence of cystic hydatid disease in Australia, and to a lesser extent alveolar hydatid disease, either contracted in Australia (*E. granulosus*) or in migrants from endemic areas overseas (*E. granulosus* and *Echinococcus multilocularis*) (Dew, 1935). There was thus a need for regular surgical intervention. It was surgeons such as Harold Dew who had an interest in the basic biology of the parasite and who published in international journals such as the "British Journal of Surgery" and "British Medical Journal" that led to widespread recognition of the research being undertaken on hydatid disease in Australia. This was enhanced by Dew's contributions in the literature (Dew, 1953) and at conferences to the debate raging at the time on whether cystic and alveolar hydatid disease were caused by the same or different species of *Echinococcus* ('dualists' versus 'monists') as well as his collaboration with researchers in Europe such as Félix Dévé.

Dew recognised the developmental differences of the two stages in the life cycle and studied the metacestode stage of the cystic and alveolar forms (Fig. 1) in depth, both in human cases and animals (Dew, 1922, 1925, 1928, 1935). He thus

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Table 1
Current taxonomy of *Echinococcus* spp.

Species	Strain/genotype	Known intermediate hosts	Known definitive hosts	Infectivity to humans
Echinococcus granulosus	Sheep/G1	Sheep (cattle, pigs, camels, goats, macropods)	Dog, fox, dingo, jackal and hyena	Yes
	Tasmanian sheep/G2	Sheep	Dog, fox	Yes
	Buffalo/G3	Buffalo	Dog	Yes
Echinococcus equinus	Horse/G4	Horses and other equines	Dog	Probably not
Echinococcus ortleppi	Cattle/G5	Cattle	Dog	Yes
Echinococcus canadensis	Cervids/G8,G10	Cervids	Wolves, dog	Yes
Echinococcus intermedius	Camel/Pig/G6/G7	Camels, pigs, sheep	Dog	Yes
Echinococcus felidis	Lion/–	Warthog (possibly zebra, wildebeest, bushpig, buffalo, various antelope, giraffe, hippopotamus)	Lion	Uncertain
Echinococcus multilocularis	Some isolate variation	Rodents, domestic and wild pig, dog, monkey	Fox, dog, cat, wolf, racoon-dog, coyote	Yes
Echinococcus shiquicus	–/–	Pika	Tibetan fox	Uncertain
Echinococcus vogeli	None reported	Rodents	Bush dog	Yes
Echinococcus oligarthrus	None reported	Rodents	Wild felids	Yes

Data from: Thompson et al. (1995), Thompson and McManus (2002), Jenkins et al. (2005b), Thompson (2008), and Carmena and Cardona (2014).

complemented much of Dévé's research undertaken in rodents (Dévé, 1919, 1946) and built on this. Dew demonstrated that an intact laminated layer was a fundamental and unique component of the 'healthy' hydatid cyst and considered this layer to be of host origin, and demonstrated that elements of the cyst wall (germinal layer) could regenerate (Dew, 1935). He realised that the cyst enclosed a sterile environment and was under intracystic pressure, and speculated on the reasons for this being indicative of viability and a function of the germinal layer. In observations of what we now know to be the metacestode of *E. multilocularis*, Dew described naked prolongations of the nucleated germinal membrane (layer) in direct contact with host tissues (Dew, 1935), a fundamental feature of the infiltrating metastatic metacestode of *E. multilocularis* (Fig. 1) subsequently described using electron microscopy 60 years later (Mehlhorn et al., 1983; and see Section 2.4). Thus it was Harold Dew that led to Australia being referred to as the 'home of hydatids' in terms of research. He paved the way for other researchers and did much to establish *Echinococcus* as a model organism. "In this country of Australia we all have unrivalled opportunities to investigate this disease, both in man and in animals, and it is our duty to contribute our share to future advances in its study" (Dew, 1935).

The economic impact and public health significance of cystic hydatid disease in Australia worsened over the next 30 years, which provided an opportunity for obtaining research funds from organisations supporting health and livestock research. J.D. Smyth obtained funds from these sources and took a physiological approach in his research aimed at increasing understanding of the developmental biology of *Echinococcus*. Having forged an interest in developing in vitro cultivation procedures for *Schistocephalus* with success in establishing much of the life cycle of this cestode in culture (Smyth, 1946, 1950), he turned his attention to *Echinococcus* (see Smyth, 1990) for which the ability to study and maintain the parasite in vitro would provide a great research tool for investigating methods of control.

The practical and ethical difficulties of undertaking in vivo studies in the canid or felid definitive hosts of *Echinococcus* further reinforced the need to develop in vitro systems. It was these pioneering studies of Smyth (Smyth et al., 1966 and reviewed in Smyth and Davies, 1974a; Howell and Smyth, 1995) that demonstrated the potential of *Echinococcus* as a model for studying principles of developmental biology, differentiation, host–parasite relationships and evolutionary biology (Smyth, 1969; Smyth et al., 1966), and which have influenced research and theoretical understanding far beyond parasitology (Thompson and Lymbery, 2013). Smyth saw the potential of exploiting *Echinococcus* as a novel model system for studying parasitism as distinct from a model for studies on evaluating anthelmintic or other anti-parasitic drugs (Smyth, 1969). He thus expanded the definition of a 'model' to embrace studies on all the biological activities that supported the

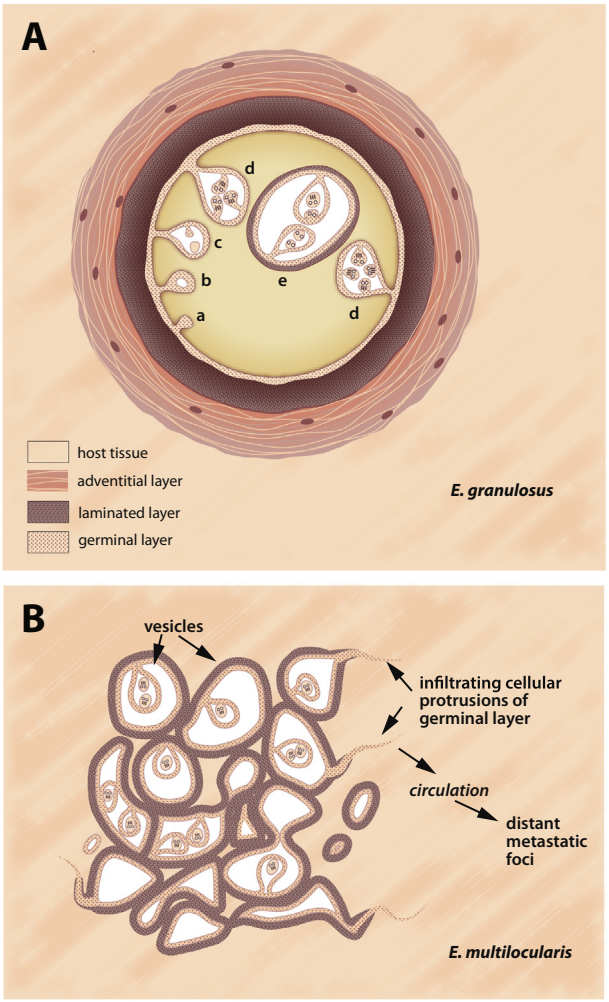

Fig. 1. Diagrams illustrating the structural differences between the metacestodes of (A) *Echinococcus granulosus* (a–d, stages in development of protoscoleces and brood capsule; e, daughter cyst) and (B) *Echinococcus multilocularis* (redrawn from Thompson, 1995).