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Twentieth century toxinology and antivenom development in Australia

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Abstract

It was not until the last decade of the 19th century that an experimental approach (led by Bancroft in Queensland and Martin in Sydney and Melbourne) brought a higher plane of scientific objectivity to usher in the modern era of Australian toxinology. This Australia era, 1895–1905, coincided with and in some respects was the result of the new knowledge emerging from Europe and the Americas of the therapeutic effects of antitoxins. The subsequent systematic study of Australian venoms and toxins through to the 1930s and beyond, by Tidswell, Fairley, Ross, Kellaway and Cleland, set the foundation for Australia's leading reputation in venom research. As elsewhere, this development was to revolutionise the medical management of those victims who in the past had died in Australia from our venomous and toxic fauna. Morgan, Graydon, Weiner, Lane and Baxter at the Commonwealth Serum Laboratories emphasised the importance of cooperation between those expert at catching and milking the venomous creatures and those developing the antivenoms. Commercial antivenom manufacture began in Australia in 1930 with the tiger snake antivenom. This was followed by other antivenoms for the other important species (1955: taipan; 1956: brown snake; 1958: death adder; 1959: Papuan black snake; 1961: sea snake; 1962: polyvalent) including the first marine antivenoms in the world (1956: stonefish antivenom; 1970: box jellyfish) culminating, in 1980, with the release of the funnel web spider antivenom. More recent activity has focused on veterinary antivenoms and production of new generation human antivenoms for export (CroFab and ViperaTAB). This paper reviews some of the milestones of Australian toxinology, and antivenom development in particular, during the 20th century.

Keywords: Toxinology; Australia; Antivenoms (antivenene); Snakebite; Poisonous plants

1. Introduction

Aboriginal men and women have lived with the world's most venomous creatures, on the land and in the seas of Australia, for some 60 millennia prior to European settlement in 1788. Across Australia, Aboriginal men and women of more than 600 language groups had developed an intimate knowledge of the toxic biota, had learned to respect it and mostly to avoid its threat (Pearn, 2001; Pearn and Winkel, 2006). For a century after colonial settlement, European scientists brought the "new" zoological and botanical knowledge to scientific notice in the wider world. Medical practitioners in particular—naval and army surgeons, surgeon-expeditionary and medical

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immigrants—established the discipline of Australian toxinology (Pearn, 1994a, b; Pearn and Winkel, 2006). This "new" knowledge of Australia's toxic biota was essentially observational, descriptive and empirical (von Mueller, 1858–1882; Krefft, 1869; Koch, 1871–1877). It was not until the last decade of the 19th century that an experimental approach (Bancroft, 1894; Lauterer, 1895; Martin, 1897a, b; Tidswell, 1899, 1900) brought a higher plane of scientific objectivity to this subject and so ushered in the modern era of Australian toxinology. This Australia era, 1895–1905, coincided with and in some respects was the result of the new knowledge emerging from Europe and the Americas of the therapeutic effects of passive immunisation with antivenene. As elsewhere, this development was to revolutionise the medical management of those victims who in the past had died in Australia from our venomous fauna. This paper reviews some of the milestones of Australian toxinology, and antivenom development in particular, from that time (Table 1).

2. A universal antivenom?

Antivenom therapy was made possible by Roux's and later Calmette's (1894) and Brasil's (1898) (Hawgood, 1992) development of passive immunisation, discoveries made possible in turn by Pasteur's (1881) earlier demonstration of active immunisation and protection of sheep against the Anthrax bacterium. The first specific application of Pasteur's principles to snake antivenom production began with Henry Sewall's experiments in Michigan whereupon he successfully injected increasing amounts of rattlesnake venom into pigeons without ill effect (Sewall, 1887). Within a few years Albert Calmette (1863–1933) had progressed this idea at the Institut Pasteur in Saigon and later in Paris and Lille (1891–1896), leading to the world's first commercially available antivenom (Calmette, 1894). The general principle of Calmette's specific discovery—that the serum of horses immunised against cobra venom would universally protect the snake bitten patient—was quickly tested in Australia.

Table 1
A chronological summary of the development of passive immunotherapy and the introduction of commercial antivenoms for the management of human envenomation in Australia

1930	Tiger Snake (*Notechis scutatus*) antivenom.
1938	Tick (*Ixodes holocyclus*) antivenom.
1956	Red-back Spider (*Latrodectus hasselti*) antivenom.
1955–62	Species-specific snake antivenoms.
1955:	taipan (*Oxyuranus scutellatus*).
1956:	brown snake (*Pseudonaja textilis*).
1958:	death adder (*Acanthophis antarcticus*).
1959:	black snake (*Pseudechis papuanus*).
1961:	sea snake (*Enhydrina schistosa*).
1959	Stonefish (*Synanceia*) antivenom.
1962	Polyvalent Snake antivenom introduced.
1970	Box jellyfish (*Chironex fleckeri*) antivenom.
1980	Funnel-web Spider (*Atrax robustus*) antivenom.

Commercial antivenoms approved for human use in Australia have all been produced by the Commonwealth Serum Laboratories (now CSL Limited), Parkville, Australia (after Sutherland, 1994). The dates provided represent the first recorded sales of the respective antivenoms as documented by Sutherland (1994) or in records held by the Australian Venom Research Unit.

Although McGarvie Smith undertook some work immunising rabbits with tiger snake venom in Sydney in 1892, and Thomas Lane Bancroft did likewise with guinea pigs in Brisbane in 1893 (Bancroft, 1893; Cann, 1986), the first major work on antivenoms in Australia came from CJ Martin. The mid-1890s, the British born Dr. (later Sir) Charles Martin (1866–1955) (Fig. 1), initially working as a Demonstrator in Physiology at the University of Sydney and later as an acting Professor of Physiology at the University of Melbourne, challenged Calmette's concept of the universality of his "antivenene". Martin tested it against the venom of both the Australian red-bellied black snake, *Pseudechis porphyriacus*, and that of the common tiger snake, *Notechis scutatus* (Martin, 1897a). He was unable to demonstrate any clinically significant venom neutralisation by this "antivenene" against these two Australian species, thus "disposing of Calmette's concept that his antivenom could be used globally" (Sutherland, 1994). Despite this, "antivenom serum" from Burroughs Wellcome and Co, London, continued to be advertised for sale in the Australasian Medical Gazette into the 20th century (see April 21, 1902 Edition) and Calmette's serum was reported as being used in Australia in 1902 (Bill, 1902). Martin made numerous other contributions to the nascent field of Australian toxinology (reviewed in Hawgood, 1997) including the first investigations into the chemistry of Australian venoms, studies of the pharmacological action of venom, particularly the effect of snake venom on blood clotting, and the nature of toxin–antitoxin relationships as well as the physiology, particularly heat regulation, of marsupials and monotremes, such as the platypus (Martin, 1892;