Krimpsiekte in South Africa: Historical perspectives

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Krimpsiekte, also known as cotyledonosis or *nenta* in sheep and goats, has been recognised as a disease entity since 1775. However, it was only in 1891 that Veterinary Surgeon Soga reproduced the condition by dosing *Cotyledon* (= *Tylecodon*) *ventricosus* leaves to goats. Professor MacOwan, a botanist, confirmed the identity of these nenta plants. From a South African veterinary toxicological point of view the date 1891 is of considerable historical significance as this was the first time that a plant was experimentally demonstrated to be toxic to livestock in South Africa. A chronological account of the history of krimpsiekte research is provided.

Introduction

Krimpsiekte, a paretic or paralytic condition in small stock, was one of the first diseases documented in South Africa and ascribed to plant poisoning. Members of three genera of the succulent Crassulaceae family (*Cotyledon*, *Tylecodon* and *Kalanchoe*), generally referred to as *plakkies*, have been incriminated as a cause of this poisoning. Krimpsiekte is a chronic form of cardiac glycoside poisoning and various cumulative bufadienolides, with neurotoxic properties unique to these compounds, have been isolated over the years (Kellerman *et al.* 2005). Krimpsiekte, which is the Afrikaans vernacular name of the disease, can be directly translated as 'shrinking disease' and refers to the neuromuscular signs. Krimpsiekte is, arguably, the most important plant poisoning of small stock in the Little Karoo and southern fringes of the Great Karoo (Kellerman, Naudé & Fourie 1996). This article provides a short synopsis of historical developments.

The early days

Historically, krimpsiekte has also been referred to as *nenta*, *t'nenta*, *t'nanta*, *c'nenta*, *rita*, cotyledonosis and *kraamsiekte* (Henning 1926; Hutcheon 1899; Steyn 1934; Watt & Breyer-Brandwijk 1962). Vahrmeijer (1981) stated that krimpsiekte or *nenta* had been a serious problem in southern Africa since 1775, but no authentic documentation confirming this could be traced. Steyn (1934) cited Browne (1864), who, in 1864, referred to a disease called *t'nanta*, as the first official record of krimpsiekte. In 1884, Hutcheon induced the disease in two goats by dosing them with strained rumen liquor obtained from a goat with krimpsiekte. In 1877, the botanist MacOwan (Figure 1), as cited by Hutcheon (1899), erroneously implicated *Lessertia annularis* Burch, a legume, as the cause of *rita* (krimpsiekte) in goats. Hutcheon also produced krimpsiekte in a dog by feeding it on the livers of affected goats. Hutcheon (1899) described the result of his feeding experiment as follows: 'The dog which was fed upon the livers developed acute symptoms of the disease in two days.' This is the first report of secondary (relay) intoxication induced by krimpsiekte.

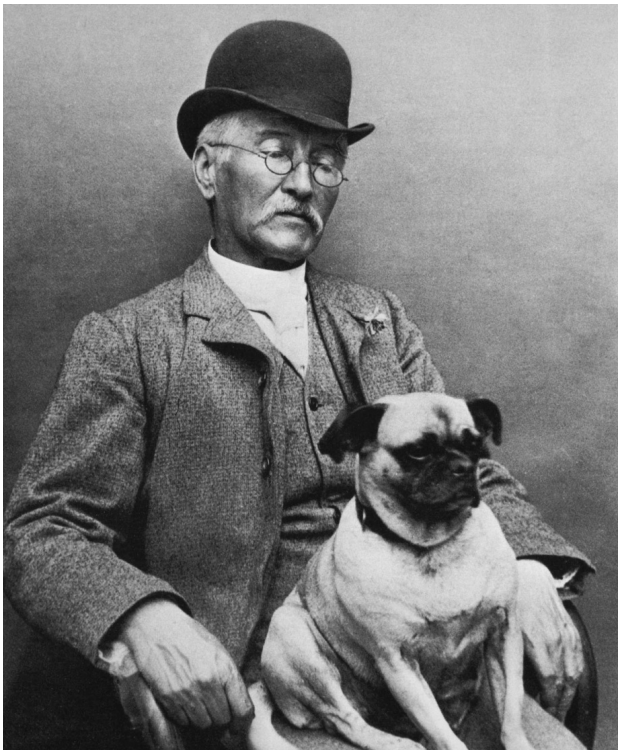
The aetiology of krimpsiekte was resolved only in 1891 when Veterinary Surgeon Soga produced the condition by dosing *Tylecodon ventricosus* leaves to goats. He determined that as little as 56.7 g (recorded as 2 oz. at the time) of freshly cut and shredded *T. ventricosus* leaves, administered on three consecutive days, caused typical signs of the disease within four days and death within six days of commencement of dosing. All of the eight goats included in the trial developed typical signs of krimpsiekte and six died (Soga 1891). In his confirmatory dosing trials, Soga credited Mr Weyer of De Toekomst, Somerset East for incriminating this plant. Professor MacOwan identified these *nenta* plants as *Cotyledon ventricosa* Burm (Soga 1891), later renamed *T. ventricosus* (Burm. f.) Tölken (Tölken 1978). From a South African veterinary toxicological point of view, the date 1891 is of considerable historical significance as this was the first time that a plant was experimentally demonstrated to be toxic to livestock in South Africa (Curson 1926).

Soga's results were nevertheless met with some scepticism because the trials were carried out with local goats in an krimpsiekte-endemic area and no member of the Crassulaceae was previously known to be toxic. Later, veterinary surgeons Tomlinson, Borthwick and Dixon independently confirmed Soga's findings by feeding or drenching *T. ventricosus* to local goats in non-krimpsiekte

areas (Hutcheon 1899). The historical photographs of goats suffering from *nenta* or krimpsiekte (Figure 2) were taken by Borthwick in 1898 (Hutcheon 1899; Watt & Breyer-Brandwijk 1962).

The 1900s

The second member of the Crassulaceae family to be implicated in poisoning was *Cotyledon orbiculata*. In 1908, Mr Burtt Davy, the Government Agrostologist and Botanist, and his herbarium assistant, Miss Stent (Figure 3), related an incident of suspected poisoning of fowls with *C. orbiculata*.

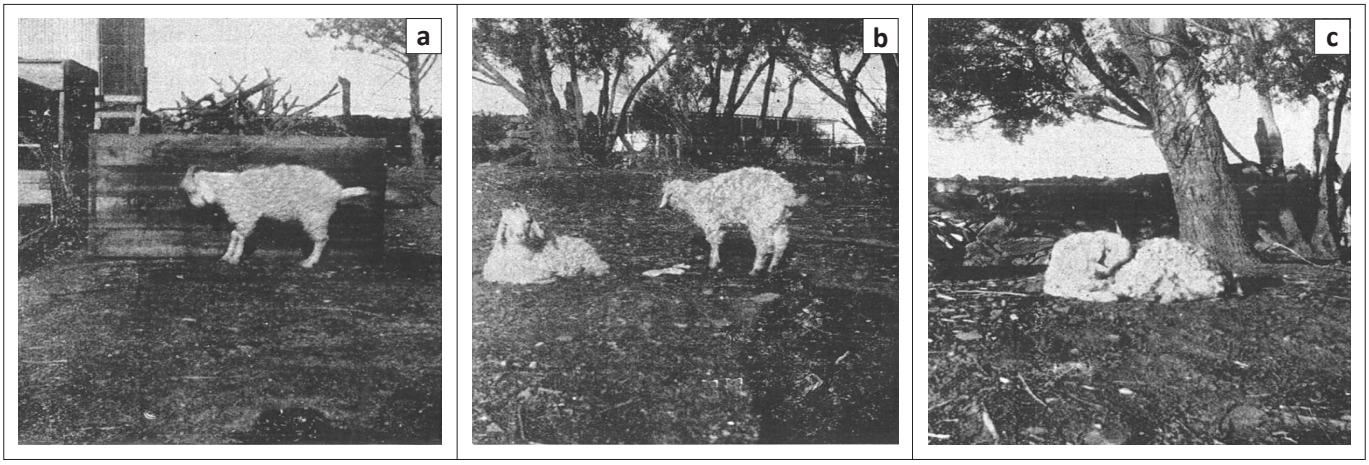


Source: McCracken, D.P. & McCracken, E.M., 1988, *The way to Kirstenbosch*, CTP Book Printers, Cape Town

FIGURE 1: Prof. Peter MacOwan (1830–1909).

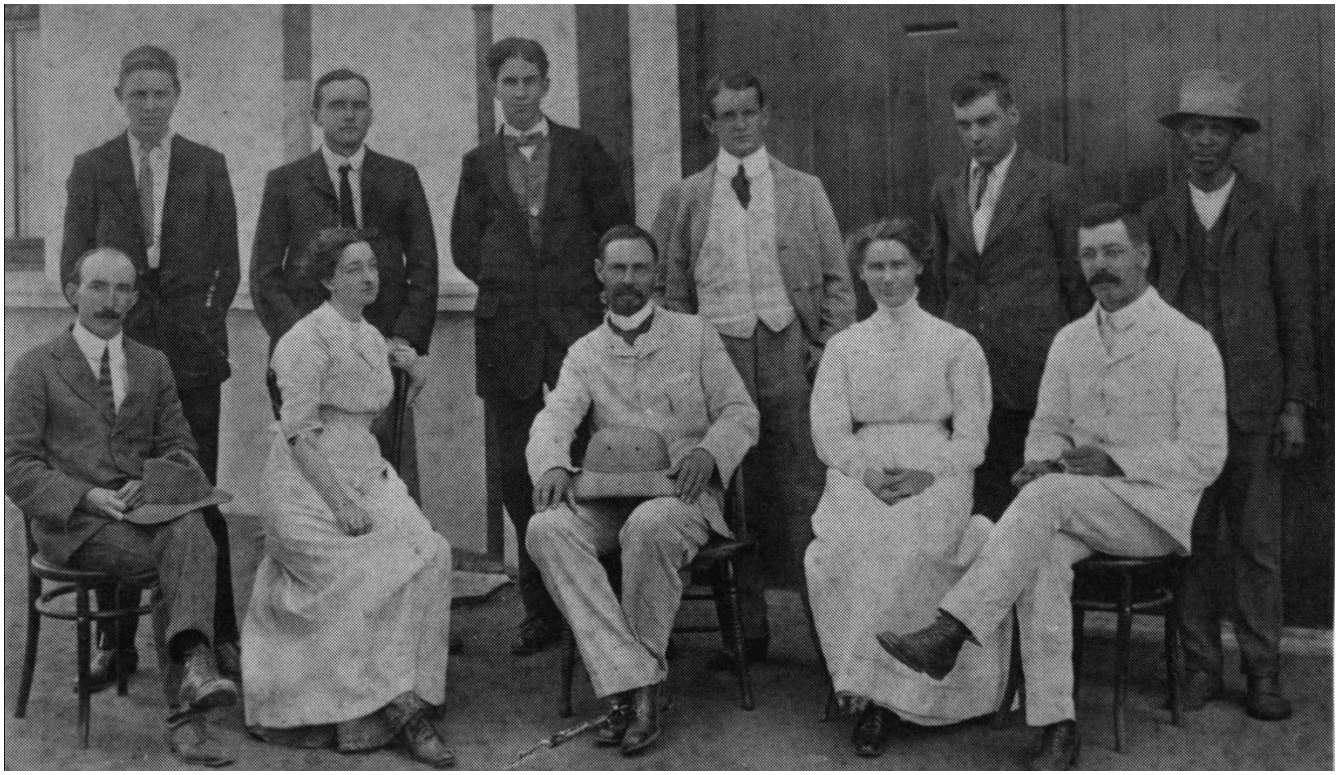
After thinning out *C. orbiculata* in her garden, a lady fed chopped leaves to her fowls. The following day six hens were dead and several others severely depressed. Burtt Davy also reported that Sir Arnold Theiler confirmed toxicity (paralysis and mortality) in two hens fed plant material obtained from the outbreak (Burtt Davy & Stent 1908). Kehoe (1912) administered 240 g *C. orbiculata* plant material to an Angora goat, which subsequently developed clinical signs reminiscent of krimpsiekte and died 10 days later. He also induced *C. orbiculata* poisoning in fowls. In small stock, *C. orbiculata* can induce both acute and chronic (krimpsiekte) intoxication under natural conditions (Terblanche & Adelaar 1965; Tustin, Thorton & Kleu 1984). Acute cardiac glycoside poisoning in a flock of 16 Angora goat rams, of which six died, occurred after consumption of *C. orbiculata* (Tustin *et al.* 1984). *C. orbiculata* collected from a farm near Maltahöhe in Namibia, where sheep developed clinical signs resembling krimpsiekte, was dosed orally to sheep to confirm toxicity. A single dose of only 1.0 g/kg of this particular batch of plant material (semi-dried stems and leaves) was lethal for sheep. Strong indications of a cumulative effect were found, with as little as 50 mg/kg plant material daily (nine dosages over 13 days) producing intoxication (Terblanche & Adelaar 1965).

The second *Tylecodon* species to be implicated in the aetiology of krimpsiekte was *Tylecodon wallichii* (Harv.) Tölken subsp. *wallichii* (previously known as *Cotyledon wallichii*. Harv.), which was proven toxic by Curson (Figure 4) in 1920 (Curson 1926; Tölken 1978). Henning (1926) confirmed that this plant was highly toxic to goats, sheep, horses and even fowls. An adult goat weighing 36 kg was drenched with 7 g dried *T. wallichii* leaves on day 0 and again on day 6, representing a total dose of only 0.39 g/kg. Clinical signs developed four days later, with mortality ensuing two days after the commencement of clinical signs. In another trial, an adult goat (38 kg) was poisoned by 17 g fresh, minced leaves administered over 25 days. A three-month-old goat kid also died within seven days of receiving 24 g minced flowers. Henning concluded that when livestock were administered relatively large doses of plant material in a comparatively



Source: Hutcheon, D., 1899, 'Nenta', *Agricultural Journal of the Cape of Good Hope* 14, 862–873

FIGURE 2: Photographs of goats suffering from krimpsiekte taken by Veterinary Surgeon Borthwick in 1898: (a) and (b) both represent the appearance of the goats when suffering from 'nenta' in the acute stage, whilst (c) represents the position they generally assume when lying down in the last stage of the disease, and in which they are usually found dead.



Source: Gunn, M. & Codd, L.E., 1981, *Botanical Exploration of southern Africa*, AA Balkema, Cape Town

FIGURE 3: Dr Joseph Burtt Davy (1870–1940), seated in the centre, and Miss Sydney Margaret Stent (1875–1942), seated to his right.

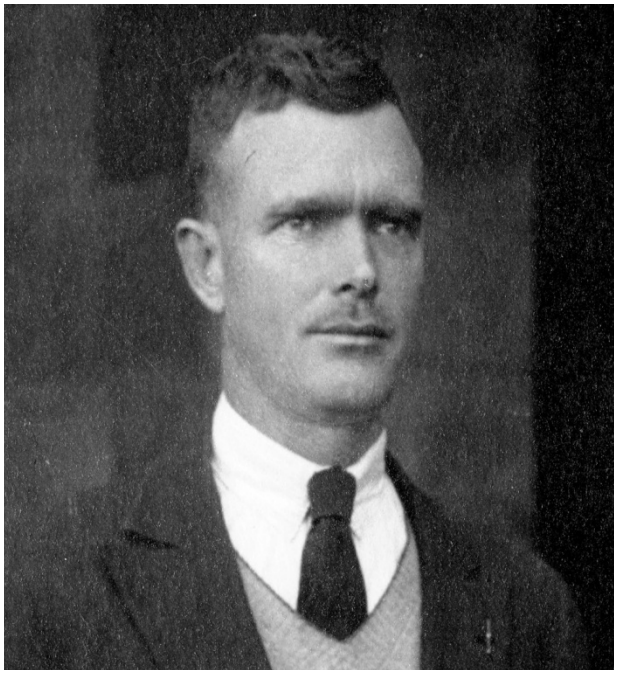
short period, acute intoxication resulted, sometimes referred to as '*opblaas*' krimpsiekte [bloating krimpsiekte] in the field. In contrast, when small doses were repeatedly given over an extended period, clinical signs more typical of krimpsiekte were produced. Henning (1926) also induced secondary poisoning in dogs by feeding them goat and horse livers and horsemeat obtained from krimpsiekte carcasses.

Acute cardiac glycoside poisoning in cattle in the winter rainfall area has been ascribed to *Tylecodon grandiflorus* (Burm. f.) Tölken (Kellerman *et al.* 2005). However, Anderson and co-workers reproduced krimpsiekte in sheep by repeated oral dosing of 0.5 g/kg – 1.0 g/kg fresh *T. grandiflorus* plant material (Anderson *et al.* 1983a).

The acute form of cardiac glycoside poisoning were also induced by dosing dead or senescent or fresh, dried *Kalanchoe lanceolata* plant material to sheep (Anderson *et al.* 1983b) and feeding stems and leaves to a cow (Masvingwe & Mavenyengwa 1997). In the sheep, acute intoxication was induced by a single dose of 3.5 g/kg – 5 g/kg milled, dried plant material. However, ovine krimpsiekte could not be induced by repeated administration of *K. lanceolata* plant material at lower doses. Mortality occurred in the cow after ingestion of approximately 15.5 g/kg fresh plant material (Anderson *et al.* 1983b; Masvingwe & Mavenyengwa 1997).

Chemistry and toxicity

The first references to a possible toxic principle appeared in 1926 when Henning (1926) noted that the toxic principle



Source: Photograph courtesy of Dr D. Verwoerd from the University of Pretoria

FIGURE 4: Dr H.H. Curson (circa 1933).

in edible tissue was thermostable, not being destroyed at 120 °C for 15 min nor by boiling in water for 30 min. He further reported that the majority of the toxin was extracted with 60% ethanol acidified with 1% HCl. In the same year Kamerman (1926), primarily utilising *C. orbiculata* plant material and comparing his results with those obtained

with other *plakkies*, isolated an amorphous, slightly bitter, colourless toxic compound found to be non-alkaloidal, non-glucosidal and nitrogen free. He assigned the provisional name cotyledontoxin ($C_{32}H_{28}O_7$) to the compound and suggested that it belonged to the picrotoxin group of nerve poisons. Gunn ([1931] cited by Steyn 1934) reported that a 70% alcohol extract of *T. ventricosus* produced a digitalis-like action on excised frog and rabbit organs. The intensity of action was about one-eighth that of digitalis (Steyn 1934).

Sapeika (1936) suggested that, besides the neurotoxic cotyledontoxin, toxic species also contained a substance, probably a glycoside, with the pharmacological properties of digitalis. The contradictory findings of Kamerman on one hand and Gunn and Sapeika on the other were resolved some 40 years later when a bufadienolide cardiac glycoside, namely cotyledoside, was isolated from *T. wallichii* (Van Rooyen & Pieterse 1968; Van Wyk 1975). The oral and subcutaneous LD_{50} of cotyledoside (at 48 h) for guinea pigs was 0.173 mg/kg and 0.116 mg/kg, respectively (Naudé & Schultz 1982). These authors also induced acute and subacute poisoning and mortality in sheep following single intravenous injections of 0.05 mg/kg – 0.1 mg/kg cotyledoside and chronic intoxication (krimpsiekte) after two to five consecutive daily intravenous administrations of 0.01 mg/kg cotyledoside (Naudé & Schultz 1982). In 1997 Botha and co-workers confirmed the presence of cotyledoside in *T. wallichii*. Two sheep were given cotyledoside (0.01 mg/kg – 0.015 mg/kg body weight) intravenously on consecutive days, except during weekends. Both sheep developed typical krimpsiekte on day nine of the experiment, which lasted until they were sacrificed (Botha *et al.* 1997).

In 1985 Anderson *et al.* isolated four bufadienolides from *C. orbiculata*, namely tyledoside C and three new bufadienolides: orbicuside A, B and C (Anderson *et al.* 1985; Steyn *et al.* 1986b). The approximate subcutaneous LD_{50} (at 24 h) of orbicusides A, B, and C and tyledoside C for guinea pigs were 0.1 mg/kg, 0.25 mg/kg, 0.25 mg/kg and 0.2 mg/kg, respectively (Anderson *et al.* 1985). Orbicuside A and tyledoside C had a mild cumulative effect in guinea pigs after four daily subcutaneous injections of 50% of the LD_{50}. Five consecutive intravenous injections of 0.012 mg/kg orbicuside A to a sheep induced ruminal stasis, paresis and recumbency (Anderson *et al.* 1985).

The toxicological properties and toxins of *T. grandiflorus* have been thoroughly investigated by Anderson and co-workers. Six bufadienolides isolated from *T. grandiflorus* were characterised as tyledosides A, B, C, D, F and G (Anderson *et al.* 1983a; Steyn *et al.* 1986a). Typical signs of krimpsiekte in a sheep were induced by repeated intravenous injection of 0.012 mg/kg tyledosides A and D. The approximate subcutaneous LD_{50} in guinea pigs of tyledosides A and D was 0.120 mg/kg, approximately 0.2 mg/kg for tyledoside C and E, and approximately 0.180 mg/kg for tyledoside F. For three of these bufadienolides, namely tyledosides A, D and F, a cumulative effect in guinea pigs could be demonstrated, but no such cumulative effects were evident with tyledosides C and E (Anderson *et al.* 1983a). In 1998, Botha *et al.* (1998) also isolated tyledoside D from *T. ventricosus* collected on a farm near Somerset East in the Eastern Cape.

The presence of cardiac glycosides in *K. lanceolata* was confirmed by the extraction and isolation of three bufadienolides: 3-*O*-acetylhellebrigenin (previously extracted from *Melianthus comosus*) and the two others (initially referred to as K 28 A and K 28 B) designated lanceotoxin A and lanceotoxin B (Anderson *et al.* 1983b; Anderson, Steyn & Van Heerden 1984). Krimpsiekte could be reproduced experimentally only by repeated intravenous administration of 0.01 mg/kg lanceotoxin B and 0.02 mg/kg lanceotoxin A. The estimated subcutaneous LD_{50} of lanceotoxin A for guinea pigs was *c.* 0.20 mg/kg, for lanceotoxin B *c.* 0.1 mg/kg and for 3-*O*-acetylhellebrigenin *c.* 0.36 mg/kg. A cumulative effect was demonstrated with lanceotoxin A and B, but 3-*O*-acetylhellebrigenin was non-cumulative (Anderson *et al.* 1983b; Anderson *et al.* 1984).

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Competing interests

The author declares that he has no financial or personal relationship(s) that may have inappropriately influenced him in writing this article.

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