

MYOTONIC DISEASES SINCE ASMUS JULIUS THOMAS THOMSEN (1815–1896) AND PETER EMIL BECKER (1908–2000)

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ABSTRACT: Julius Thomsen first published his account of myotonia (an unusual muscle stiffness disorder) in himself and his family in 1876. By November 1971, Peter Becker was already famous for his eponymous Becker muscular dystrophy when he came to the Second International Congress on Muscle Diseases, in Perth. There, he presented an extensive study of myotonia, recognising a recessively inherited disease (now known as Becker's recessive generalised myotonia), distinct from Thomsen's myotonia congenita and clearly distinguishable from Steinert's myotonic dystrophy, both dominantly inherited. Peter Becker, Shirley Bryant, Reinhardt Rüdel and Allan Bretag all met in Perth, with mutual interests in myotonia. They subsequently maintained contact while Bretag undertook research in Germany in 1972–1973 and 1977. Later, in 1978, Bretag worked with Bryant's myotonic goats in Cincinnati. His research on Thomsen's and Becker's myotonias has since progressed to confirmation of Bryant's *chloride hypothesis* through a molecular genetic study of the muscle chloride channel, CLC-1. This has culminated in several collaborative papers with German colleagues and, finally, in a mechanistic description of how the CLC-1 channel is gated.

Keywords: Thomsen, Becker, myotonia, Cl⁻ channel, gating

Asmus Julius Thomas Thomsen (Figure 1) was born in 1815 in Brunsholm in the Parish of Esgrus on the Angeln Peninsula in the Danish Duchy of Slesvig (from the mid-1860s annexed into Prussian Schleswig-Holstein). After early private tuition and later attending Slesvig's Cathedral school, he undertook his university studies in Kiel, Berlin and Copenhagen, and obtained his medical doctorate from Kiel in 1839. He returned to the Angeln Peninsula to practise medicine and was appointed Kreisphysikus (district physician) in Kappeln on the Schlei River in 1853 (Lanska et al. 1990), eventually being awarded the German medical practitioner's title 'Sanitätsrat' (Member of the Board of Health) in 1885 (Nissen Family Collection, courtesy of Kristina Wiberg¹). It was from there in 1876 that he was provoked into publishing an earlier-prepared manuscript on the muscle cramping and stiffness disease afflicting himself and his family, after spending much of his life concealing it, because his youngest son was accused of malingering to avoid military service. It was entitled 'Tonische Krämpfe in willkürlich beweglichen Muskeln infolge von ererbter psychischer Disposition (Ataxia Muscularis?)' [Tonic Cramps in Voluntary Muscles as a Consequence of a Hereditary Psychological Trait (Ataxia Muscularis?)].



Figure 1: Asmus Julius Thomas Thomsen (courtesy of Kristina Wiberg¹, from the Nissen Family Collection) and his signature 'Dr Kreisphysikus, J Thomsen' (from Thomsen's letter accepting his 1853 appointment as district physician in Kappeln, courtesy of the Landesarchiv Schleswig-Holstein, Abt. 309 Nr. 27 973).

In this work Thomsen gave his own clinical history and described his symptoms: an initial painless but incapacitating cramping of muscles – myotonia – following the first exertion after rest. From quite young, he had found it impossible to leave his chair quickly, if called upon unexpectedly. On standing up, his leg cramps prevented him from walking and, if he struggled to walk, he would fall, rigid for a time. Soon, the involuntary stiffness would subside and upon repeating the movements he could move as quickly as other boys of his age, and, he claimed, with better endurance. He wrote that he had often been chastised or even physically punished by those without insight or understanding of the condition, having a generally negative influence on his psyche and personality and causing him much irritability. There was an associated muscular hypertrophy and the disease did not worsen with age but Thomsen felt that its symptoms were exacerbated by cold and concluded, mistakenly, that it could be attributed to a familial neurosis caused by central nervous system dysfunction. Its dominantly transmitted hereditary nature was obvious from his own genealogical research, where he traced it in 16 of 28 family members from his great grandmother down to his own children. Between times, Thomsen published works in a variety of other medical fields, on abortifacients, narcotics, poisons and on population health in the Faroe Islands and Iceland. Interestingly, he was also an accomplished translator, especially of Norwegian and Danish into German, and a prolific and respected poet, several of his poems being set to music by Heinrich Marschner, some even alluding to his ‘evil’ affliction (Lanska et al. 1990). Within a few years, his strange and rare disease was widely known as Thomsen’s disease or myotonia congenita (MC). Thomsen’s own descriptor, ‘ataxia muscularis’, was not favoured because of the absence of ataxic, uncoordinated movement. Also, despite initial controversy, it has since been conclusively shown to be a wholly muscular disorder with no central nervous system involvement, any neurosis in Thomsen’s family most likely unrelated to the myotonia or perhaps caused by the stresses of coping with and hiding the involuntary myotonic cramps. Following the description

of *atrophischer Myotonie* (myotonic dystrophy, DM), however, in which muscle wasting, cognitive impairment, cataracts, frontal balding and other systemic involvement accompanied the myotonia (Steinert 1909, 1910), there was considerable confusion and debate over whether Thomsen’s MC and Steinert’s DM were distinctive disease identities or constituted a spectrum of features of a single disease. To a certain extent, the mystery continues to the present day (discussed below).

So-called ‘nervous’ or ‘fainting’, but actually ‘myotonic’ goats, (Figure 2) were known in Texas and Tennessee since the early 1900s, and Shirley Bryant, in Cincinnati, obtained the first clue to the aetiology of myotonia from them (Bryant 1962). He had purchased some of these goats in Tennessee which, when startled, would become stiff and wooden and, if off balance at the time, would topple over just as occurs in Thomsen’s MC. Voluntary, electrical or mechanical stimulation of human and goat myotonic muscle was known to produce an abnormal prolonged sequence of action potentials in the electromyogram. Action potentials are the electrical impulses that control the contraction of a muscle and their characteristics are determined by the flow of positively charged sodium and potassium ions and negatively charged chloride (Cl^-) ions back and forth through myriads of ion channels in the muscle cell membranes, specific proteins making up the channels for each different ion type. Normally, sequences of muscle action potentials terminate instantly when stimulation ends and do not continue on into *after-discharges*. Bryant found that biopsied normal goat muscle, deprived of Cl^- in its bathing solution, produced the abnormal after-discharges of action potentials in response to stimulation, just like those occurring in myotonic goat muscle bathed in a control solution containing Cl^- . From further research, he developed his *chloride hypothesis*, proposing that myotonic muscle cell membranes were, for some reason, impermeable to Cl^- ions leading to electrical instability and, hence, to the prolonged electrical activity and delayed relaxation (Bryant 1969). In turn, this involuntary exercise would cause the muscular hypertrophy seen in MC. By the late 1960s and early 1970s, Allan Bretag in Adelaide



Figure 2: Myotonic goats, standing, being chased by Shirley Bryant and fallen rigidly cramped.

(Bretag & Potter 1969) and Reinhardt Rüdel in Heidelberg (Rüdel & Senges 1971) were showing that myotonic electrical activity and prolonged contractions could also be induced in rat muscle biopsies by replacing Cl^- in their bath solutions with any of a number of different anions or by adding substances presumed to block Cl^- permeation of the muscle cell membrane. Bretag also used a computer model to show how reducing trans-membrane Cl^- current would induce myotonic electrical activity in muscle, but not in nerve, (Bretag 1971).

At the Second International Congress on Muscle Diseases held in Perth, Australia, in 1971, and in his impressive 1977 monograph on the subject, Peter Emil Becker (1908–2000) finally clarified some of the distinctions between Thomsen's MC and other syndromes associated with myotonia (Becker 1971, 1977). In particular, he convincingly described a new myotonic condition, recessively rather than dominantly inherited, now known as Becker's recessive generalised myotonia (RGM). Becker had studied 142 propositus families, 27 with dominant inheritance and 104 with inheritance that was evidently recessive, the remainder described as 'uncertain' (Becker 1977). Among those with dominant inheritance, he examined members of Thomsen's extended family. Based on prior reports of Dr Karl Nissen (Thomsen's grand nephew who, too, had the condition), Dr Rolf Nissen (Karl Nissen's foster son) and Dr Eivind Thomasen, and with their ongoing help, Becker published a very large kindred containing 68 persons who had all inherited the condition from Thomsen's great grandmother, Frederikke Christiane Ludovika von Barner née von Grambow, (Becker 1977; Lanska, et al. 1990). Becker also examined 149 patients from the recessive group, noting distinctive differences from Thomsen's MC. Onset was gradual and later during childhood but symptoms became more severe than in MC, often worsening well into adulthood. Despite more muscular hypertrophy, unexpected muscular weakness typically followed the initial myotonic stiffness. Becker also commented on a thinness, or even atrophy, of neck and forearm muscles in up to 25% of cases. Nevertheless,

he termed both Thomsen's MC and this recessive myotonia *nondystrophic*, by comparison with the dominantly inherited DM of Steinert. Recently, the issue of muscle pathology in the nondystrophic myotonias has been revisited using magnetic resonance imaging (Morrow et al. 2013).

Becker, Bretag, Bryant and Rüdel (Figure 3) met for the first time at the Perth Congress where they discussed their mutual research interests in myotonia. Of the four, Peter Becker was already famous for his studies on muscular dystrophy, especially of a type of Duchenne muscular dystrophy, also X-linked, but milder and with a longer life expectancy (Becker muscular dystrophy, Becker & Kiener 1955). Born in Hamburg in 1908, Becker had studied medicine at several universities in Germany and Austria and graduated in 1933. His early career is clouded and his life has not been without controversy (Becker 1985; Hill 2013). In the mid 1930s he worked under the notorious promoter of eugenics Eugen Fischer, and with Fischer's staunch disciple, Fritz Lenz, at the Kaiser Wilhelm Institute in Berlin. In 1933 he became a member of the SA (Brownshirts) and joined the Nazi Party in 1938 (Hill 2013). From the late 1930s, apart from a brief period as a doctor in the Luftwaffe, he was employed in the University Psychiatric Hospital in Freiburg, where he began his work on muscular dystrophies. After World War II, he was dismissed for his membership of the Nazi organisations but was officially 'de-nazified' in 1948 (Hill 2013). He subsequently practised neurology in Tuttlingen, was reinstated to lecture each week in Freiburg and was appointed professor in 1951. In 1957, he succeeded Fritz Lenz as Chair of Human Genetics at the Georg-August-University of Göttingen, establishing and leading its Institute of Human Genetics from 1962 until his retirement in 1975 (Becker 1985).

After the Perth Congress, Reinhardt Rüdel and colleagues made extensive biophysical studies of human muscle cell membranes in biopsies taken from people with MC (Rüdel & Lehmann-Horn 1985). These isolated but living biopsies were maintained in a solution developed

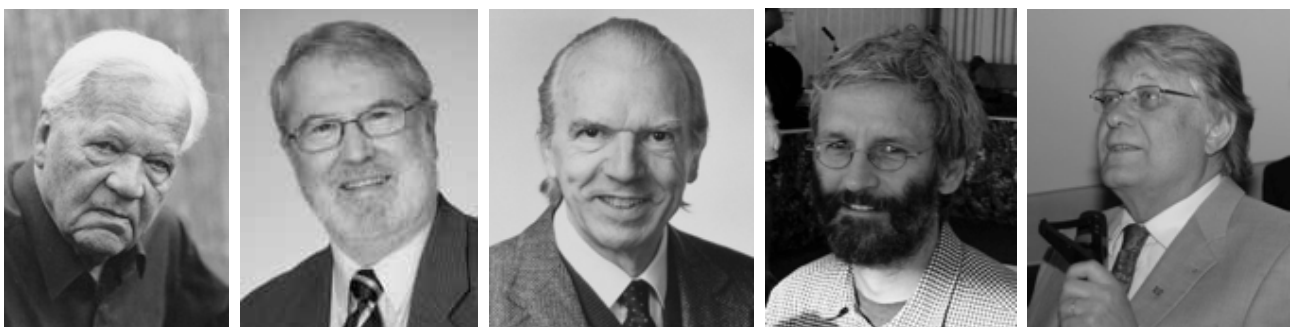


Figure 3: From left, Peter Becker, Allan Bretag, Shirley Bryant, Thomas Jentsch and Reinhardt Rüdel.

by Allan Bretag to mimic the natural interstitial fluid that surrounds every muscle cell in the body; a fluid that is in equilibrium with blood plasma across the walls of blood capillaries (Bretag 1969). By 1987, the hypothesised Cl^- permeation pores of muscle cell membranes had undergone major biophysical and pharmacological characterisation and many of their properties had been compared with other known ion channels (Bretag 1987). Actual muscle Cl^- channel proteins, however, had still not been directly observed. This next step occurred in 1991 when Thomas Jentsch (Figure 3) and colleagues at the Centre for Molecular Neurobiology in Hamburg cloned the rat gene, *Clcn1*, coding for the skeletal muscle Cl^- channel, CLC-1, and began to characterise the protein using voltage clamp methods after its heterologous expression in *Xenopus* oocytes (Steinmeyer et al. 1991). It was soon proven that both MC and RGM result from specific mutations in human *CLCN1* (Koch et al. 1992; George et al. 1993) and hundreds of disease-associated variants are now known (Bretag 2015). Entirely different genes were associated with DM1 and DM2 (DM's two forms, reviewed by Meola 2013) but, just as in MC, the myotonia in DM1 turned out to be due to a relative absence of normally functional CLC-1 channels (Mankodi et al. 2002). Surprisingly, other dominantly inherited myotonias, closely mimicking Thomsen's MC, were associated, not with a lack of normal Cl^- channels, but with malfunctioning muscle sodium channels coded by mutated *SCN4A* genes (McClatchey et al. 1992; Heine et al. 1993). Mutations in *CLCN1* have also been found in myotonic goats and in myotonic mice, dogs, buffalo and horses (reviewed in Bretag 2015).

Soon after Jentsch and his group in Hamburg had cloned the rat Cl^- channel gene, Bretag and his colleagues in Adelaide began a collaboration with them. Detailed investigation of the structure and function of CLC-1 channels, their response to pharmacological agents and foreign anions and the specific dysfunctions of mutated CLC-1 has followed (e.g. Astill et al. 1996; Rychkov et al. 1996, 1998; Aromataris et al. 2001). Initial biochemical and biophysical investigations suggested that CLC-1 channels exist as 'double-barrelled' dimers (see Figure 4) composed of two identical subunits (Fahlke et al. 1997) each with its own trans-membrane Cl^- conducting pore (Saviane et al. 1999). Among many other original and unusual findings contributed by the above studies, the pores in CLC-1 turned out to be gated (opened and closed) by the Cl^- ion itself. The higher the concentration of Cl^- at each external channel mouth, the more likely it was to bind at the channel gate and open it to the flow of Cl^- and vice versa (Rychkov et al. 1996). Earlier known ion channels were gated by the binding of a neurotransmitter, or drug, to the channel protein or were gated solely by changes in the

voltage across the cell membrane. Secondly, the double-barrelled arrangement of the CLC-1 channel allowed for two different gating processes: an independent fast gating of each of the two pores, and a slower process, where both pores closed simultaneously for a period of time before opening to independent operation again (Saviane et al. 1999). This latter common gating process appeared to require a considerable overall structural rearrangement of both subunits (Bennetts et al. 2001). Thirdly, anions other than Cl^- were found to alter both ion permeation through the channel and gating (Rychkov et al. 1998). Finally, an improved understanding of Thomsen's MC and Becker's RGM at the molecular genetic level came from *CLCN1* mutations discovered in two Australian patients with MC. In these necessarily heterozygous patients, CLC-1 would have existed as dimers composed of 'wild-type' (wt) and mutant (mt) subunits combined in the proportions, wt-wt : mt-mt : wt-mt = 1 : 1 : 2. These mutants were investigated after expression in *Xenopus* oocytes by Jentsch's Hamburg laboratory in an international (German, French, Australian) collaborative study (Kubisch et al. 1998). Compared with normal homo-dimers (wt-wt), gating in these particular mutant homo-dimers (mt-mt) was severely disrupted so that the gates seldom opened. Gating was also subverted by the presence of these mt subunits in hetero-dimers (wt-mt), their wt subunit pores also rarely opening. This clarified what was genetically known as the *dominant negative effect*, myotonia being inevitable when numbers of functioning Cl^- pores were reduced towards 25% of normal. For some *CLCN1* mutations from mild MC and RGM patients, the mt subunits had less, or no, effect,

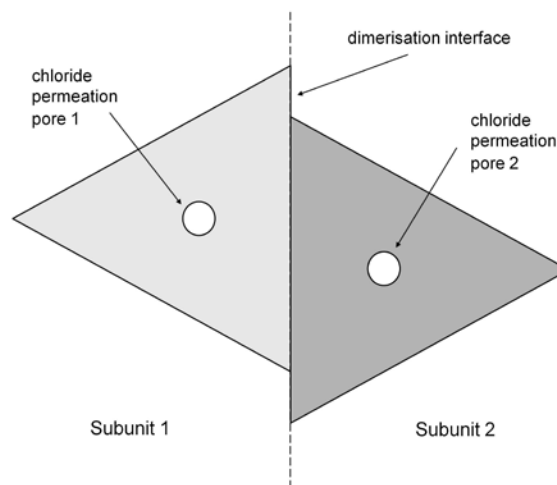


Figure 4: Viewed from above the surface of the cell membrane, the pseudo-symmetrical arrangement of identical CLC-1 protein monomers (subunits) is shown making up the functional chloride channel dimer. Subunits bind tightly to each other at a specialised dimerisation interface. One chloride permeation pathway through each subunit connects the cell's exterior to its interior, creating a functionally 'double-barrelled' structure.

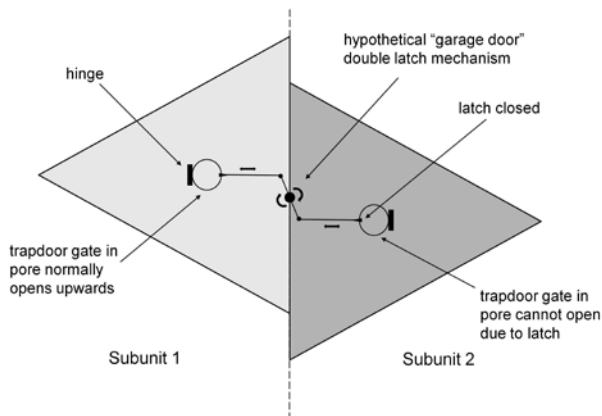


Figure 5: A hypothetical common gating linkage crosses the dimerisation interface and acts to latch or unlatch both 'fast' gate trapdoors simultaneously.

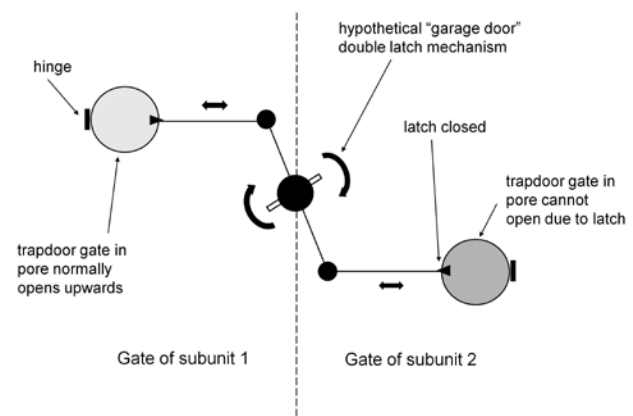


Figure 6: Detail of the hypothetical common gating linkage showing the common gate in the closed state.

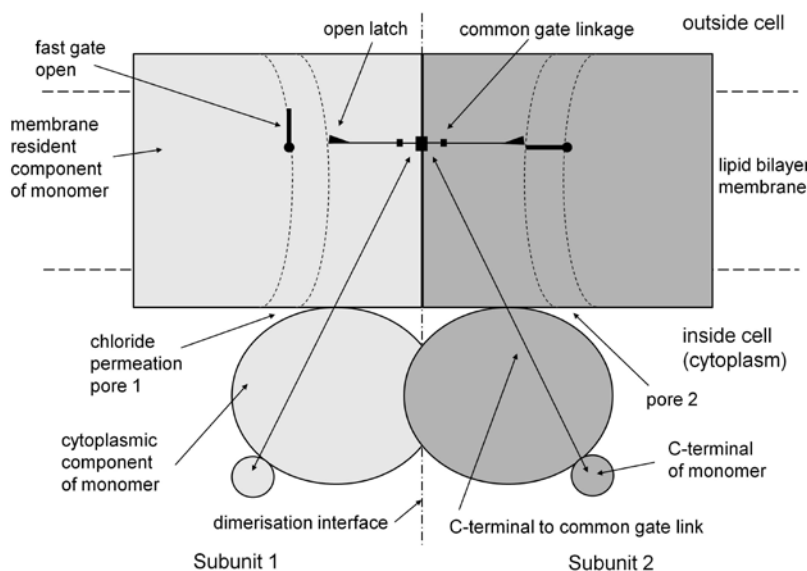


Figure 7: A representation of the CLC-1 dimer from the front within the cell membrane and viewed along the dimerisation interface. The triangular prisms of the monomeric protein subunits float like icebergs within the lipid bilayer of the membrane, their lower extensions are shown as globules within the cytoplasm of the cell. One chloride pore per subunit is indicated by the dotted lines passing between the interior and exterior of the cell. With the common gate open, the common gating linkage is unlatched so that the fast gates can operate independently, the one on the left is shown as open and that on the right is closed. There is some connection between the C-terminal of each monomer and the common gate link as shown by the double-headed arrows.

respectively, on their wt partners. Heterozygous parents of RGM patients could thus have up to 50% of normal Cl^- conductance, sufficient to be symptom free, while severe RGM patients might have zero functional CLC-1 channels, with a range of Cl^- conductance and disease severity in between.

When Roderick MacKinnon and his colleagues in New York determined the x-ray crystal structure of protein relatives of CLC-1, their dimeric structure was confirmed, with two identical subunits and one Cl^- pore per subunit in a pseudo-symmetrical, double-barrelled arrangement (Dutzler et al. 2002; Feng et al. 2010) (Figure 4). Elucidation of the gating mechanisms of these channels then became possible. The biophysically-observed 'fast gate' in each of the two channel pores (Figures 5–7) proved to be the carboxyl side chain of a glutamate residue that could swing in and out of the individual Cl^- conducting pathways (Dutzler et al. 2003). Many naturally occurring MC mutations were found in residues clustered near

the CLC-1 dimerisation interface, providing a clue to the common gating mechanism (Figures 4, 7) with site-directed mutagenesis then being used to confirm the involvement of this protein region (Duffield et al. 2003; Cederholm et al. 2010). In a subsequent collaboration with Jie Zheng in Davis, California, fluorescence resonance energy transfer (FRET) showed that common gating was, indeed, associated with concerted rearrangements within the CLC-1 dimer (Ma et al. 2011): the two cytoplasmic C-terminals separating on closure of the common gate and approaching each other when it opened. Neither common gating nor fast gating occurred if the fast gate carboxyl side chains were eliminated by site-directed mutagenesis (Cederholm et al. 2010). Using FRET, however, it could be shown that the conformational changes associated with common gating were unaffected by these carboxyl deletions (Ma et al. 2011). This proved that it was the fast gates that had to be the final effectors of the common gating mechanism. From these studies it became apparent that the

so-called ‘common gate’ of the CLC-1 proteins was not a separate gate that closed both pores at a site away from the individual fast gates but was simply a mechanism that simultaneously locked both fast gates shut (Ma et al. 2011; Bennetts & Parker 2013) (Figures 5–7).

Exactly how the common gating mechanism communicates between each fast gate, to ensure that both are locked shut at the same time, remains uncertain but the pseudo-symmetrical arrangement of the two subunits when viewed from vertically above can provide an analogy: the ‘garage door’, double-latching mechanism (Figures 5, 6). In this case, the dominant negative effect could result from the latching mechanism in a mutated subunit being faulty, making unlatching of its fast gate difficult. By being mechanically connected to its normal partner subunit’s fast gate, overall unlocking (common gate opening) would be harder to achieve.

Finally, in a culmination of German–Australian parallel and collaborative research in this field, both Michael Pusch and Allan Bretag have written complementary chapters for the CRC *Handbook of Ion Channels*: Pusch’s chapter is titled ‘CLC chloride channels and transporters’, and Bretag’s ‘CLC-related proteins in diseases’ (Zifarelli & Pusch 2015; Bretag & Ma 2015).

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Endnote

- 1 Kristina Wiberg is related to Thomsen through her mother, Elsa Vikling née Nissen (see also page 61).