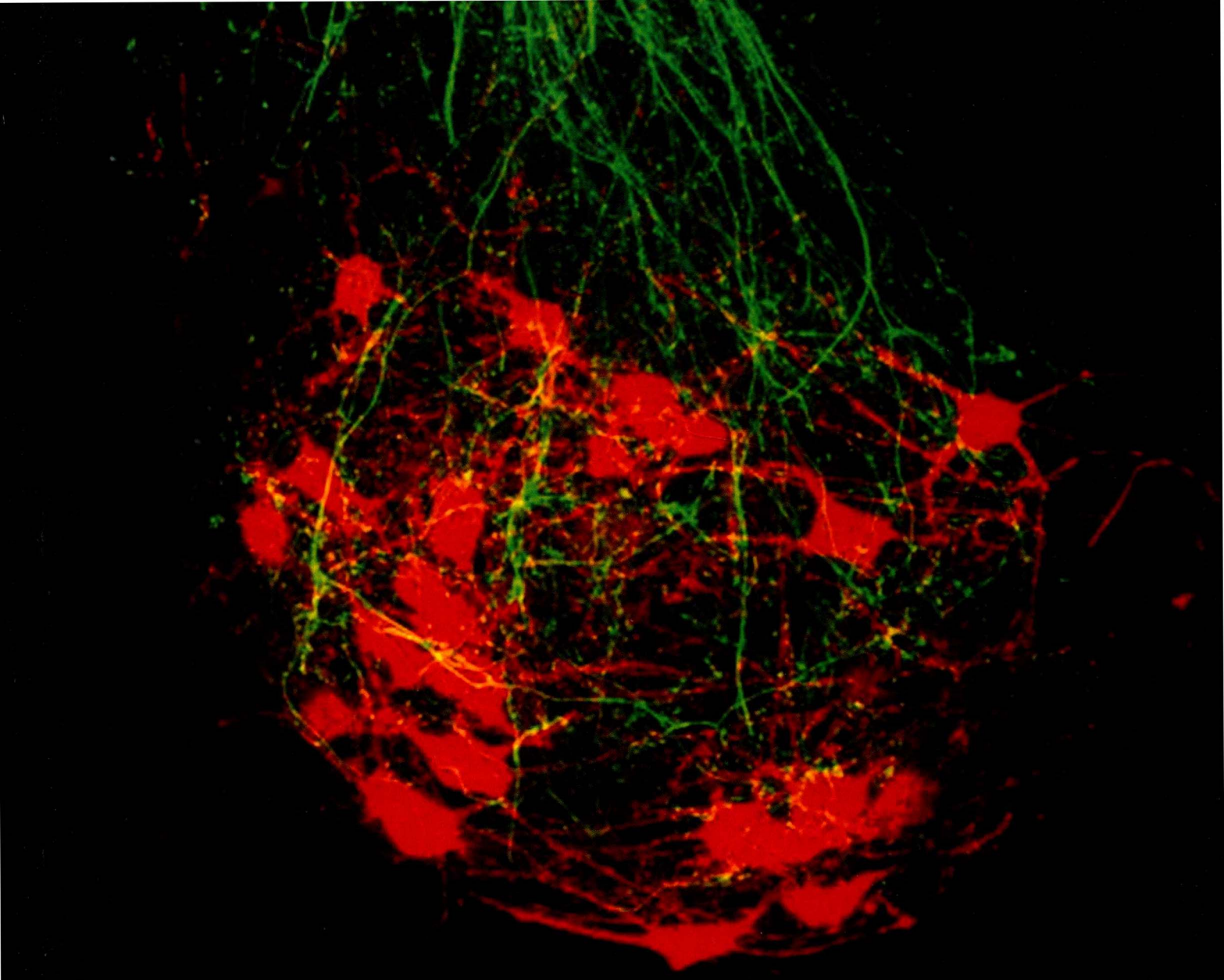

Spinal Muscular Atrophy

Disease Mechanisms and Therapy

Edited by

Charlotte J. Sumner, Sergey Paushkin, and Chien-Ping Ko

SPINAL MUSCULAR ATROPHY

DISEASE MECHANISMS AND THERAPY

Edited by

CHARLOTTE J. SUMNER
Johns Hopkins University School of Medicine, Baltimore, MD, United States

SERGEY PAUSHKIN
Spinal Muscular Atrophy (SMA) Foundation, New York, NY, United States

CHIEN-PING KO
University of Southern California, Los Angeles, CA, United States

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Front cover, top image: Proprioceptive sensory fibers making synaptic contacts with somata and dendrites of motor neurons in the spinal cord of a wild-type mouse. Proprioceptive fibers were labeled with Fluorescein dextran (in green) and the motor neurons were labeled with Texas Red dextran (in red) by retrograde fill from the dorsal root and ventral root, respectively.

Front and back cover, bottom image: Spinal motor neurons in the 1st, 2nd, and 3rd lumbar segments (labeled respectively in blue with Cascade Blue dextran, in red with Texas Red dextran, and in green with Alexa-488 dextran) in the rostro-caudal aspect visualized by retrograde fill from each perspective ventral root.

Images courtesy of Dr. George Mentis, Motor Neuron Center, Columbia University, New York, NY.

Back cover photo: Emily Lozina, type 1, 2/11/11 – 12/18/15, courtesy of Jennifer Lozina.

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List of Contributors

E.J. Androphy Indiana University School of Medicine, Indianapolis, IN, United States

W.D. Arnold The Ohio State University, Columbus, OH, United States

C.E. Beattie Ohio State University, Columbus, OH, United States

T. Bordet Biotherapies Institute for Rare Diseases, Evry, France

P.J. Boyd University of Edinburgh, Edinburgh, United Kingdom

A.H.M. Burghes The Ohio State University, Columbus, OH, United States

M.E.R. Butchbach Nemours Alfred I. duPont Hospital for Children, Wilmington, DE, United States

A.N. Calder Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

K.S. Chen Spinal Muscular Atrophy (SMA) Foundation, New York, NY, United States

J.J. Cherry RaNA Therapeutics, Cambridge, MA, United States

S.P. Corti IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

T.O. Crawford Johns Hopkins University School of Medicine, Baltimore, MD, United States

B.T. Darras Boston Children's Hospital, Boston, MA, United States

D.C. De Vivo Columbia University Medical Center, New York, NY, United States

M.O. Deguise Ottawa Hospital Research Institute, Ottawa, ON, Canada; University of Ottawa, Ottawa, ON, Canada

C.J. DiDonato Feinberg School of Medicine, Chicago, IL, United States; Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States

G. Dreyfuss HHMI University of Pennsylvania School of Medicine, Philadelphia, PA, United States

V. Dubowitz UCL Institute of Child Health, London, United Kingdom

A.D. Ebert Medical College of Wisconsin, Milwaukee, WI, United States

I. Faravelli IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

R.S. Finkel Nemours Children's Hospital, Orlando, FL, United States

K.H. Fischbeck National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, MD, United States

E.V. Fletcher Columbia University Medical Center, New York, NY, United States

K.D. Foust The Ohio State University, Columbus, OH, United States

E.L. Garcia University of North Carolina, Chapel Hill, NC, United States

T.H. Gillingwater University of Edinburgh, Edinburgh, United Kingdom

D. Hammers University of Florida, Gainesville, FL, United States

L.T. Hao Ohio State University, Columbus, OH, United States

A.C. Hart Brown University, Providence, RI, United States

K.J. Hodgetts Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

M.D. Howell Iowa State University, Ames, IA, United States

Y. Hua Shantou University Medical College, Shantou, Guangdong, China; Soochow University, Suzhou, Jiangsu, China

S.T. Iannaccone University of Texas Southwestern Medical Center, Dallas, TX, United States

J. Jarecki Cure SMA, Elk Grove Village, IL, United States

B.K. Kaspar The Ohio State University, Columbus, OH, United States

S.J. Kolb The Ohio State University, Columbus, OH, United States

L. Kong Johns Hopkins University School of Medicine, Baltimore, MD, United States

R. Kothary Ottawa Hospital Research Institute, Ottawa, ON, Canada; University of Ottawa, Ottawa, ON, Canada

A.R. Krainer Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, United States

V. Le Verche Spinal Muscular Atrophy (SMA) Foundation, New York, NY, United States

C.L. Lorson University of Missouri, Columbia, MO, United States

C.M. Lutz The Jackson Laboratory, Bar Harbor, ME, United States

A. MacKenzie CHEO Research Institute, Ottawa, ON, Canada

A.G. Matera University of North Carolina, Chapel Hill, NC, United States

E.S. Mazzone Università Cattolica del Sacro Cuore, Largo Gemelli, Rome, Italy

V.L. McGovern The Ohio State University, Columbus, OH, United States

J. Melki University of Paris Saclay, Le Kremlin-Bicêtre, Paris, France

N. Mendoza-Ferreira University of Cologne, Cologne, Germany

G.Z. Mentis Columbia University Medical Center, New York, NY, United States

E. Mercuri Università Cattolica del Sacro Cuore, Largo Gemelli, Rome, Italy

S. Messina University of Messina, Messina, Italy

U.R. Monani Columbia University Medical Center, New York, NY, United States

J. Montes Columbia University, New York, NY, United States

L.L. Nelson University of Texas Southwestern Medical Center, Dallas, TX, United States

S.Y. Ng Harvard University, Cambridge, MA, United States

P. O'Hern Brown University, Providence, RI, United States

M.A. Osborne The Jackson Laboratory, Bar Harbor, ME, United States

M. Oskoui McGill University Health Center, Montreal, QC, Canada

T.N. Patitucci Medical College of Wisconsin, Milwaukee, WI, United States

S. Paushkin Spinal Muscular Atrophy (SMA) Foundation, New York, NY, United States

L. Pellizzoni Columbia University Medical Center, New York, NY, United States

M.J. Pérez-García Vall d'Hebrón Research Institute, Barcelona, Spain

T.W. Prior The Ohio State University, Columbus, OH, United States

R.M. Pruss Windhover Biomed Ltd., London, United Kingdom

L.L. Rubin Harvard University, Cambridge, MA, United States

S.B. Rutkove Beth Israel Deaconess Medical Center, Boston, MA, United States

M.K. Schroth University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

L.R. Simard University of Manitoba, Winnipeg, MB, Canada

N.N. Singh Iowa State University, Ames, IA, United States

R.N. Singh Iowa State University, Ames, IA, United States

B.R. So HHMI University of Pennsylvania School of Medicine, Philadelphia, PA, United States

C.J. Sumner Johns Hopkins University School of Medicine, Baltimore, MD, United States

S.S. Sunshine Spinal Muscular Atrophy (SMA) Foundation, New York, NY, United States

H.L. Sweeney University of Florida, Gainesville, FL, United States

S. Tisdale Columbia University Medical Center, New York, NY, United States

E.F. Tizzano Vall d'Hebrón Research Institute, Barcelona, Spain; Vall d'Hebrón Hospital, Barcelona, Spain

L. Torres-Benito University of Cologne, Cologne, Germany

B. Wirth University of Cologne, Cologne, Germany

Z. Zhang HHMI University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Preface

Since mid-1980s, we have witnessed a boom in the identification of genes underlying neurological diseases, but there are only few diseases for which this knowledge has led to efficacious treatment for patients. Spinal muscular atrophy (SMA) may soon become one such disease. SMA is the leading inherited cause of infant mortality characterized by motor neuron loss and muscle atrophy. The identification of the causative gene *survival motor neuron 1* (*SMN1*) by Dr. Judith Melki and colleagues in 1995 galvanized the SMA community and attracted many individuals from different disciplines to join the fight against SMA. As a result, the SMA community has witnessed significant advances in both basic and clinical research. At the time of the writing of this book, there are about 20 drugs in development including six in clinical trials. Remarkably, we now stand on the brink of the first FDA-approved treatment for this devastating neurodegenerative disease. Given the complexity of the disease, the diverse research approaches involved, the unique advances in therapeutic development, and the increasing body of literature on SMA, we felt that the time has come for the first comprehensive book on SMA. We envision that this book will become the single "go to" textbook for graduate and medical students, as well as an essential reference for academic and biotech/pharma researchers, clinical researchers and practitioners, and patients and their advocacy organizations. We also hope that this integrated, thorough review will enable further advancements in SMA basic research, therapeutics development, and patient care. Finally, this book may be valuable to researchers and clinicians who may want to apply SMA research strategies, therapeutic approaches, and lessons learned to advance treatment for other diseases.

The book is comprised of 26 chapters organized into five sections and represents an international effort by leading SMA researchers and clinicians, whose interests and expertise encompass a wide spectrum of topics and disciplines. Chapters were written to bridge multiple disciplines and to promote effective communication between basic scientists, clinical researchers, and health care providers on the latest development in SMA. Each chapter includes an introduction, historical background, and comprehensive review of the topic, as well as outstanding questions for future investigations and key references for additional detailed study.

Section I describes the clinical features, diagnosis, and standards of care for SMA patients. It also details the development and pathology of the motor unit in SMA patients.

Section II focuses on molecular mechanisms of SMA, including transcription and splicing regulation of the *SMN* genes and the functions of the SMN protein. These molecular mechanisms are critical for providing both insights into the biology of SMN and the foundation for rational design of potential therapeutics. This section also covers cellular mechanisms underlying the disease, an effective therapeutic window with respect to the temporal requirement of SMN, and disease modifiers.

Section III details the cellular and animal models, which are indispensable for understanding the disease mechanisms and developing therapeutics in SMA.

Section IV is dedicated to SMA therapeutics development and covers the various strategies employed to date. This section also highlights the remarkable collaborative effort involving academic researchers, industry teams, advocacy organizations, and government, as well as SMA patients.

Section V focuses on advances in clinical research, including natural history studies, motor function scales and outcome measures, and biomarkers. The section concludes with lessons learned in clinical trials.

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Charlotte J. Sumner, MD
Sergey Paushkin, MD, PhD
Chien-Ping Ko, PhD

Perspectives

Sixty Years of Spinal Muscular Atrophy: A Personal Odyssey

V. Dubowitz

UCL Institute of Child Health, London, United Kingdom

We live in exciting times, and it has been a tremendous privilege to witness the remarkable growth in interest in the neuromuscular disorders over the past half-century and the quantum leap since mid-1990s in resolving the complex genetic background of spinal muscular atrophy (SMA),now on the cusp of potential therapy.

This comprehensive, state-of-the-art textbook, covering all aspects of SMA, is very timely and should provide a springboard for further efforts and advances in the future.

I shall give a broad overview of the progress of events since mid-1950s, with an inevitable personal bias of my own journey, ranging from the recognition of the various clinical forms of the disease, through the early history, amazing clinical acumen, and descriptive prowess of our forebears, to the genetic revelations in the past few decades and the potential for gene manipulation in providing a potential therapy for the disease in the future.

My first exposure to neuromuscular disorders was in a 3-week temporary locum post in 1957 at Queen Mary's Hospital for Children, south of London, where they had 2 wards of 16 beds each for long-term care of muscular dystrophy and associated disorders. I came for 3 weeks and stayed for 3 years and became committed to a career in pediatrics and a lifetime focus on muscle disorders.

At that time there was a well-defined severe infantile SMA, which had already been described at the turn of the century and had the eponymous title of Werdnig–Hoffmann disease.[1,2] Onset was at birth or in the first weeks of life and death usually in the first year.

Half a century later, a late-onset, adolescent or early-adult, ambulant form of SMA was documented in the 1950s and given the eponymous title of Kugelberg–Welander disease.[3]

From early on I noted several cases with a late infantile onset after the child had achieved the ability to sit. They then seemed to develop severe weakness of the legs and never achieved the ability to stand independently. I documented 12 such cases in 1964,[4] and it was of particular interest that several of them had had an affected younger sibling who had died in the first year of life with a classical severe infantile SMA, confirmed in some at autopsy.

In addition, the first case I diagnosed of this intermediate severity had a younger sister who had a similar onset with reluctance to stand or walk, but her parents encouraged her, and she achieved the ability to stand and to walk and then remained ambulant and fairly stable until her first pregnancy at 21 years of age, after which she lost the ability to walk independently. Of special interest as well was how static many of these intermediate cases were, with no obvious deterioration. I personally followed this initial case for 33 years and, apart from some increase in scoliosis and a need for intermittent supportive oxygen therapy, he had shown very little change over the years.[5(p334)]

At a guest lecture at the Children's Hospital of Washington in 1967, I suggested that the severe infantile SMA and the mild late-onset ambulant form might be opposite ends of a continuous spectrum of severity, given the intermediate group with variable severity from the severe to the mild end and the fact that clinical variants of the disease could occur in the same sibship.[6]

CLASSIFICATION

The medical profession has an obsession with trying to pigeonhole diseases into compartments and draw up classifications, which have no advantage unless they clarify rather than confuse.

There are no specific "types" of SMA, and the introduction of types 1, 2, and 3 was suggested by a committee of clinicians and geneticists in 1990 to promote collaborative studies between different centers and to identify the genes for SMA.[7] Their classification was based primarily on the age of onset and the age of death. I disagreed with this approach, as the age of onset was extremely variable in relation to individual severity and patients do not normally present at clinic with a death certificate. I tried to convince the committee that we should base the diagnosis entirely on the severity of the individual patient, so there would be a severe group, an intermediate group, and a mild group, and the broad distinctions could be the ability to sit unaided and the ability to stand and walk unaided. This was (somewhat reluctantly) added on to the "types." This is a classic example of a committee trying to design a horse and ending up with a camel.

I also tried to get the committee to include in the diagnostic criteria for the severe form, the one cardinal feature, which is sparing of the diaphragm in association with the severe weakness of the intercostal muscles. This results in the classical abdominal breathing and the bell-shaped chest with very little expansion. SMA is, in fact, the only neuromuscular disease that spares the diaphragm and affects the intercostal muscles and can be confidently diagnosed on this one clinical sign. I failed to convince them.

Of additional clinical interest is that in contrast to the consistent involvement of the limbs, there is sparing of the facial muscles so that these infants have a normal expression and facial mobility and also have a normal intellect. The committee was prepared to include the presence of facial weakness as an exclusion criterion.

In order to vent my frustration, I then wrote a commentary on the chaos in the classification of SMA.[8] I subsequently had *several* discussions with my neurology colleagues, and on one occasion I suddenly had a eureka moment, "If you want to designate patients on a numerical basis, perhaps your 1, 2, 3 division is not sufficiently sensitive and you should perhaps go into a decimal classification to concede the range of change within each group." After giving it some further thought and introducing it at our clinic, it became apparent that it was a very practical way of documenting very accurately the grade of involvement of the patient. I then wrote a sequel to my "chaos" paper.[9]

I also *recalled* two remarkable children I had seen during the 1950s with horrendous scoliosis, were able to "sit" in a semi-recumbent position, and were borderline between the severe and the intermediate group. They survived 8 and 10 years, respectively, and had a remarkable sparing of the face as well as normal intellect (see illustrations[5(p340)]).

As with any other assessment of particular features in infants, one should first define the middle of the range and then it becomes easy to complete the rest. Therefore, if one looks at type 1.5 as the child who is floppy from early infancy and has mainly abdominal breathing with collapse of the chest but no spontaneous respiratory difficulties, apart from when there is a superadded chest infection, then type 1.1 would be an infant who was severely paralyzed at birth, had severe respiratory involvement, and might require ventilator support.

At the other end of the scale a 1.9 would be a child almost able to sit independently but not quite and needing some support, and having much better respiratory function.

In the intermediate group, type 2.5 would be middle of the range for the intermediate group, sitting with stability and good posture; whereas 2.1 would be a child barely able to maintain a sitting position and type 2.9 would be a child with ability to stand with support but not independently.

In the ambulant group, 3.5 would be a reasonably steady ambulation; whereas 3.1 would be just able to stand and walk independently and 3.9 would be on the verge of normal but perhaps unable to walk fast, to hop on one leg, or to run.

Type 4.0 would be normal and there is no real advantage in trying to subdivide further on the basis of age between an earlier-onset type 3 up to the age of 20 years and a later-onset type 4, beyond 20 years, and possibly dichotomizing siblings on either side of the artificial divide.

Since that time, we have consistently used this scoring system within our muscle unit and found it to be particularly sensitive to assessing the specific status of an individual patient. It should also be of great use when conducting clinical trials. Because of the relatively stable situation in SMA (of all severities), one would need to see an actual improvement in function to be confident of a response. This would be quite impossible to base on a "type" related to age of onset as this is extremely variable, and about a third of cases of the classical severe SMA (types 1.2–1.5) may have an antenatal onset and not require ventilation at birth.

The disease is relatively stable but some patients may show deterioration with time and lose ability to sit independently or to walk, but should still retain their original designation. In the severe group one also notes marked deterioration at times following an acute respiratory infection, leaving more severe and general weakness, including the face. Marked loss of function may also follow severe infections in the intermediate group.

Another interesting clinical feature that we frequently observed in the intermediate SMA children, was a very fine tremor of the hands. We did routine electrocardiograms on all children attending our neuromuscular clinic and frequently got a note from the cardiology department, apologizing for the artifact in the baseline of the ECG. This actually reflected the fine tremor in the muscles and was a potential marker for intermediate SMA.[5(p335)]

Another remarkable feature is the relatively acute and rapid onset of the severe cases and then a fairly steady state with no obvious loss of any residual function that they have. I had one personal experience of this. *In* Sheffield during the 1960s a woman was admitted in labor, who had had three previous infants affected by SMA and dying in first year of life. I saw the infant soon after birth and he seemed fully active with no apparent weakness and normal muscle tone and a normal response of the Moro and other neonatal reflexes. I reviewed him every day through the first week and there was no change, so discharged him. At routine follow-up at 6 weeks he was completely paralyzed, with the classical distribution of severe SMA. His mother related that this had come on fairly suddenly one night, and there was no concern

when put to sleep but in the morning was completely paralyzed.

A more severe group with marked in utero weakness and needing ventilator support at birth and with either death in utero or in the early infancy, was designated as "prenatal" SMA.[10] But this again is confusing, based on time of onset rather than severity, given that a proportion of classical type 1 cases may have a prenatal onset. I suggested that it might be more appropriate to designate this *very severe* group as SMA 0 and one could then define a 0.1 as death in utero and a 0.9 as born with severe respiratory difficulties but almost managing without ventilation. A 0.5 would have severe respiratory difficulty at birth requiring ventilator support and also more severe weakness, which can be more generalized and also associated with facial weakness, as well as more marked contractures of limbs.[11]

A RAMBLE THROUGH THE HISTORY OF SPINAL MUSCULAR ATROPHY

In addition to my interest in the clinical spectrum and management of SMA, I also have a special interest in medical history and have spent many an interesting few hours in the bowels of the Royal Society of Medicine of London Library, poring into the superb descriptions by our forebears of these interesting neuromuscular diseases.

In a 2009 review of the history of SMA[12] I came to three main conclusions:

1. **If someone's name is attached to a disease, he or she is usually the second person to have described the disease.**
2. **If you discover something new, do not read the early literature. It has all been described before. Far safer to just stick to Pub-Med, which covers the past 40–50 years.**
3. **If you quote historical papers always read the originals.**

Although the names of Werdnig and Hoffmann have been associated with the severe infantile form of SMA, they did not describe the severe form but the milder, intermediate form.

In 1891 Guido Werdnig of the Department of Pathological Anatomy in the University of Graz in Austria described two brothers with onset of weakness around 10 months.[1] One had complicating pertussis and hydrocephalus and died at 3 years. The other survived till 6 years. At autopsy he found degeneration of the anterior horn cells of the cord. Werdnig wrote a further review in 1894,[13] but subsequently made very little further contribution to the medical literature.

In contrast, Johan Hoffmann, a protégé and later successor of Erb in the medical clinic in Heidelberg, was a prolific medical author on a wide range of subjects, including SMA.

In a series of three seminal papers on SMA in the Deutsches Archiv fur Nervenheilkunde in 1893, 1897, and 1900,[2,14,15] he reviewed Werdnig's two cases and added seven of his own from three further families. He also included excellent illustrations of the histology of the muscle and central nervous system and showed the degeneration of the anterior horn cells of the spinal cord. In his 1897 paper, Hoffmann included three sequential pictures of a girl with intermediate severity SMA, which he appropriately acknowledged to come from a paper by Thomson and Bruce in the first issue of the newly established Edinburgh Hospital Reports in 1893.[16]

Their case is a typical intermediate severity SMA, with ability to sit unaided and the sequential pictures show the progression of her scoliosis. When I revisited the original Thomson and Bruce publication, I was also interested to note in the first picture of the child that it clearly shows hyperextension of her fingers, which I thought I may have been the first to observe and highlight in my 1964 series of cases, together with joint laxity, which might account for the rapid progression of scoliosis.[4]

Therefore, although Werdnig was indeed the first to publish a case of SMA of intermediate severity, Thomson and Bruce had also followed their case in parallel with Werdnig from 1889 and wrote a more extended and better illustrated report, both clinically and pathologically.[16]

The first detailed description of the severe form of SMA was by Beevor in Brain in 1903.[17] Beevor's case was the fourth affected infant in a family of eight children and the three previous cases had all died by 6 months. He drew attention to the associated intercostal weakness and sparing of the diaphragm. The diagnosis was confirmed at autopsy with degeneration of the anterior horn cells of the cord.

The first clinical picture I have found of the severe form of SMA, showing the classical jug-handle posture of the arms with flexion and internal rotation, together with the wasting and retraction of the intercostals and activity of the diaphragm, was in a personal copy of the second edition of the pediatric textbook of Jonathan Hutchinson published in 1910.[18] I was able to verify the inclusion of the same figure in the first edition of the book in 1904.

The mild ambulant form of SMA was comprehensively documented by Kugelberg and Welander[3] in an American journal, *Archives of Neurology and Psychiatry (Chicago)*, in a series of 12 cases presenting like a limb girdle muscular dystrophy but shown to be neurogenic on electromyography and muscle biopsy. An almost equivalent series from three families was published by another Swedish group, Wohlfart, Eliasson, and Fex a year earlier[19] in a Scandinavian journal, *Acta Psychiatrica*

et Neurologica (Kjobenhavn). They found associated neurogenic changes in the muscle and suggested this might be a mild variant of Werdnig–Hoffmann disease. Indeed, Kugelberg and Welander referred to the publication of Wohlfart's group and both groups had also presented cases at several clinical meetings prior to the two definitive publications.

Another key publication in the SMA field was a monograph written by Sven Brandt in 1950[20] for his medical doctorate thesis and comprising 112 cases from 89 Danish families, with 97 being under one year. A large proportion were of the severe form but some also conformed to the intermediate. He also included a number of classical pictures of the severe form.

Finally, there is one more twist to the tale. In 1899 Sylvestre[21] presented a single case at the pediatric society of Paris of a 2-month-old infant with flaccid paralysis of all four limbs and trunk since birth and weakness of the intercostals, but sparing of the diaphragm. This was the sixth child in the family and the third and fifth had been similarly affected and died at 3 and 5 months. The case report, without any illustrations, was published in the first issue of the newly established *Bulletins de la Société de Pédiatrie de Paris*. Had it not been for the sparing of the diaphragm one would not have been sure of this being an SMA rather than a congenital dystrophy or one of the severe congenital myopathies.

THE NEW DAWN

The next important milestone in SMA was the location in 1990 of the gene for SMA initially by Gilliam's group in New York in an Amish group of large families with the mild variant[22] and soon after by Melki's group in Paris.[23] It was shortly after that the same gene locus could be confirmed for the severe form both by Gilliam[24] (with whom we collaborated) and also by Melki.[25] In the same year a working group of clinicians and geneticists from both sides of the Atlantic was convened in New York to define the clinical criteria for diagnosis and exclusion of SMA and to coordinate the collaborative molecular genetic studies, which I referred to earlier.[7]

It took another 5 years until the gene was isolated and characterized by Melki's group,[26] a novel gene which they named *survival motor neuron* (*SMN*) gene. It was a complex gene as this part of chromosome 5 is duplicated and a normal individual has two copies of the gene, an active *SMN1* gene and an inactive *SMN2*. Severe cases have a deletion of exon 7 of the active gene and no change in *SMN2*. Milder cases also have deletion of exon 7 of *SMN1* but have an increased copy number of *SMN2* which provides some compensation for the deficit in *SMN1*.

One of the spin-offs of the discovery of the gene was that the geneticists were now able to diagnose absence of the *SMN1* gene in cases previously unrecognized as SMA, as they had an atypical presentation with exclusion criteria such as generalized weakness, facial weakness, and an in utero onset with even more severe and generalized weakness, and respiratory failure than the classical severe SMA.

In the current era of therapeutic trials, we have to accept that SMA is a relatively static disease (at all levels of severity) and that one would have to demonstrate an improvement in individual cases, irrespective of their severity. From a prognostic point of view the only single sign of relevance in the severe cases is the intercostal weakness and compromise of respiratory reserve. Any beneficial therapy would have to show improvement in the shape and mobility of the chest in addition to the respiratory function.

AND ONE FINAL AFTERTHOUGHT ...

There has recently been a trend in talking of the change in natural history of a disease following the introduction of supportive and potentially therapeutic treatment. I have suggested that this is a desecration of the Queen's English.[27] The natural history of a disease is the natural history, that is the course of a disease without intervention. If one is going to have a changing natural history, we shall soon be describing the natural history in each country depending on resources, in each part of a country and each center depending on facilities and expertise. What changes in relation to treatment is the prognosis for the disease or the course or outcome. Life is difficult enough getting consensus in the medical profession without introducing shifting goalposts.

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Advances in Spinal Muscular Atrophy Research

J. Melki

University of Paris Saclay, Le Kremlin-Bicêtre, Paris, France

Spinal muscular atrophy (SMA) is a genetically heterogeneous group of inherited neuromuscular disorders characterized by defect of motor neurons of the spinal cord leading to progressive atrophy and weakness of skeletal muscles. When Professors Jean Frezal and Arnold Munnich proposed to me to run a project aiming at identifying the genetic basis of autosomal recessive SMA, with the support of the Association Française contre les Myopathies (AFM), I was very enthusiastic and hoped that this project should solve the following challenges facing the field at that time (1) at the clinical level, invasive procedures were necessary to support the diagnosis of SMA including electromyographic study and/or muscle biopsy; (2) carriers of the disease had a recurrent risk of 25% of having another child affected without possible prenatal or pre-implantation genetic diagnosis to help families; and (3) no therapeutic options. Our team identified the survival motor neuron 1 (*SMN1*) gene as responsible, when mutated, for SMA in 1995,[1] after an extensive search due to the complexity of the 5q13 region, which is characterized by an inverted duplication of a large element (about 500 kb) containing several genes. The telomeric copy contains the *SMN1* gene and the centromeric copy contains a highly homologous gene called *SMN2*; both genes are transcribed. SMA is caused by deletion or conversion of *SMN1* gene in 93% of cases. The only functionally relevant difference between the two genes identified to date is a silent C→T mutation in exon 7 of *SMN2*, which determines an alternative spliced isoform that predominantly excludes exon 7[1] through a disruption of an exon splicing enhancer and the creation of an exon splicing silencer element.[2,3] The truncated transcript lacking exon 7 encodes a putative shorter and in vivo unstable protein.[4] To prove that this gene was indeed the disease gene, the identification of intragenic *SMN1* mutations was essential and was reported in our initial report[1] as well as thanks to a fruitful collaboration with Montserrat Baiget[5] reporting the first frameshift and premature stop codon in *SMN1* gene in unrelated patients. The identification of *SMN1* gene greatly improved diagnostic testing avoiding invasive procedure and family-planning options of SMA patients and carriers. Then we provided the first evidence for a tight inverted correlation between the *SMN2* copy number (and therefore the amount of the full-length protein encoded by this gene) and the clinical severity of human SMA disease thanks to the collaboration with Gideon Dreyfuss leading us to define *SMN2* as an attractive target for therapy in SMA.[6] The discovery that Gems are associated with Cajal bodies, nuclear domains implicated in the assembly, and modification of RNPs, provided the first link of SMN to RNA processing, which remains the most likely affected pathway.[7–9]

Currently, the main targets for therapeutics in SMA are aimed at increasing SMN levels by regulating *SMN2* transcription or splicing, or by using gene therapy. These approaches include gene therapy for *SMN* replacement,[10,11] antisense oligonucleotides (ASOs) to modify *SMN2* splicing,[12,13] small molecules to modify *SMN2* splicing,[14] to increase the stability of SMN protein, or to activate the *SMN2* promoter.[15] Other therapeutic possibilities such as stem cells that can differentiate into motor neurons,[16] neuroprotective agents,[17] and the use of targets downstream of SMN (once defined) are alternative attractive therapeutic strategies.

What will be the best targets for SMA therapy? Potential therapeutic benefit in SMA may depend on several factors. What is the capacity of the remaining mutant motor neurons to reinnervate skeletal muscle fibers? The functional diversity of motor neurons is well known, but little is known about the subgroups of motor neurons targeted by SMN protein deficiency as shown by the marked involvement of intercostal and axial muscles and the sparing of the diaphragm. Another question is whether there is a defect of motor neurons development, a progressive loss of motor neurons or both. In addition, animal models provided evidence that SMA pathology is not restricted to motor neurons but rather is a composite of pathology involving, in addition to motor neurons, skeletal muscle, neuromuscular junctions,[18–20] and sensory-motor neurotransmission.[21] Finally, what is/are the main targets of SMN leading to SMA? These questions are critical for the design of therapeutic strategies: when, how, and which cell types should be targeted? This reinforces the need, in parallel to therapeutic research and development, to fill the gap between *SMN1* gene defect,

RNA metabolism, the unknown relevant target(s) to date, and the resulting SMA phenotype.

This book is written by experts who contribute to major progress in the fields of SMA from the clinical features, molecular mechanisms, animal models, therapeutic developments to clinical trials. I have no doubt that this book will become an indispensable resource for clinicians and scientists having the goal to cure SMA.

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