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**PHYSIOLOGY  
CANADA**

**PHYSIOLOGIE  
CANADA**

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Announcement

Annual Meeting

The Canadian Physiological Society

Mont Tremblant, Quebec

January 10 - 15, 2001

From the Editor

With this issue, we enter a new era, in which Physiology Canada will be published on the Canadian Physiological Society web-page. This is in accordance with a decision made at the Society's annual business meeting in January (see the minutes of the meeting on page 8). This presents challenges, but also opportunities. One of the challenges will be to find ways of distributing the information to members and other interested parties who do not have convenient access to the web. We will be canvassing members to learn whether this poses a significant problem. Another challenge will be to remind members to go to the web-page to access the journal, and I will probably resort to e-mail messages to the membership when the new issues are published.

I am looking into the opportunities, to see how we can take advantage of the new publication mode to improve the content and accessibility of our journal, and I invite any comments and suggestions from our readers.

Ken Marshall

**Annual General Meeting Canadian Physiological Society  
January 22<sup>nd</sup> 2000, Chateau Lake Louise**

The meeting was called to order by the president, Dr. Tessa Gordon. Twenty eight members were in attendance.

1) Approval of the Minutes of the 1999 Annual General Meeting.

With one correction changing Bill Cupples to Will Cupples the minutes were approved

Motion to approve: Proposed: Dr. C. McIntosh, Seconded: Dr. D. Jones  
Carried

2) Treasurer's report. Dr. D. Rasmusson.

The balance for the 1999 year shows a deficit of \$253.97 this is due to the payment of the Stevenson Lecturer's expenses from the General Account rather than the designated Endowment account otherwise the balance for the 1999 fiscal year would have been \$1,113.15. This will be corrected in 2000. One of the major expenses in 1999 was the mail out of the Membership Directory, in future this will be published on the web site.

Motion to approve: Proposed: Dr. J. Lund, Seconded: Dr. D. Jones  
Carried

3) Membership:

New members:

Regular membership: Dr. P. Torkkeli, Dalhousie University, Dr. A. Braun, University of Calgary, Dr. P. Linsdell, Dalhousie University, Dr. R., Loutenizer, University of Calgary.

Student membership: J.A. Pospisilik, University of British Columbia, Y. Aoyagi, University of Alberta, N. Gaudreault, University of British Columbia, L. Yip, University of British Columbia, J. Ehses, University of British Columbia, V. Cheung, University of British Columbia, V. MacDermid, Queen's University, J. Zhang, University of Saskatchewan, R. Peterson-Wakeman, University of Saskatchewan, G. Thompson, Dalhousie University

Pending payment: T. Anderson Queen's University

Emeritus: Dr. K. Krnjevic, McGill University; Dr. J.V. Milligan, Queen's University; Dr. J. Le Blanc, Laval University.

The Society is continuing to decrease in numbers with a total membership of 382, of these 243 are regular members. Dr. T. Gordon indicated that the Heads of Departments of Physiology across Canada should encourage their Faculty to become members. The incoming President, Dr. Jim Thornhill, will be in contact with the Department Heads concerning this matter. Dr. Doug. Jones asked what was the outcome of the discussions with the Exercise Physiology Society concerning their proposed merger with CPS. After some discussion the answer was that this would not be taking place. On the matter of joint meetings, the Exercise Physiologists meet in October and this time conflicts with a number of other meetings including Neuroscience and American Heart.

4) Report on ballot re publication of abstracts in Canadian Journal of Physiology and Pharmacology.

The ballots received were: Against publication 46 For publication 38

This confirmed the vote taken at the AGM held in Cornerbrook and as a result the abstracts for the Winter Meeting will no longer be published in CJPP. Dr. Es. Sanders indicated that while he accepted the majority vote he was disappointed personally that the abstracts would no longer be published in our National Journal and be available for anyone to read. It was suggested that the way to deal with this was to publish the abstracts on the web, then they will once again be freely available.

5) Report from the Canadian Journal of Physiology and Pharmacology.

Dr. Susan Jacobs, Co- Editor, indicated that the introduction of the free CD as a bribe for rapid return of reviews has markedly improved the process with 70% being returned within the 2 week limit. The move to web publication has been completed and an alert service is in place where subscribers can receive advance notice of upcoming articles. Most Universities have taken the web subscription service. Dr. Jacobs then addressed the low rate of publication in the Journal by members of CPS.

The questions at issue were considered to be the following:

a. Low visibility. This is untrue, the journal is indexed in Medline and by other services and is as easy to access as all the "major" journals.

b. Granting Agencies. The low impact factor is considered a problem in most Granting Agencies with some considering publication in CJPP as a negative factor. If members considered publishing one paper per year in the journal while continuing to publish in higher impact journals such as AJP, J. Physiol. there is not a problem in maintaining funding levels.

c. Low Impact factor: If the impact factor is compared to other general physiological journals i.e. J. Physiol and Am. J. Physiol. it is not in fact much lower. It is only in comparison to Nature, Science etc. that the Journal suffers. It is hoped that removing the time lag between acceptance and publication and publishing review articles will increase the impact factor.

Finally Dr. Jacobs pointed out one reason for publishing in the Journal was the absence of page charges and called on members of the Society to support their National Journal.

Dr.Q. Pitman complemented CJPP on the range of music offered with the free CDs.

6) Report from Physiology Canada

Dr. Ken Marshall thanked Dr. Phillip Hicks for the smooth transition for the 30<sup>th</sup> Volume of the Journal. The increase in costs of the journal came in part from the increase in the number of pages caused by an increase in the number of abstracts and the inclusion of symposia at the current Winter Meeting. Dr. Marshall indicated that CPS should discuss whether a web version of the Journal should be initiated and whether this would replace the hard copy. He would encourage all Departments to submit for publication the abstracts of recent Ph.D. theses and up-to-date "Correspondence from Departments". Book reviews and articles on Education are also encouraged.

After some discussion a move towards a web version was favoured with the aim of replacing the hard copy. Dr. Marshall will gather information on the number of subscribers likely to be affected by the move to the web and also the current Library subscribers.

7) Future Meetings

2001 – Jointly organized by the University of Montreal and McGill University.

Dr. Al. Shrier reported that the probable location is Mont Tremblant. Further information will be available prior to the publication of Physiology Canada.

2002 – To be organized by the University of Alberta.

Dr. Es. Sanders reported that there had been a suggestion that the meeting could be held in Jasper although this is a 4 hour bus ride from Edmonton. He will have full details at the next Winter meeting.

A new Scientific Programme Committee (SPC) has been struck to work with the Local Organizing Committees and had its first meeting on Friday 21<sup>st</sup> January. The SPC recommends there be a maximum of two symposia/meeting. The SPC will also work to help the Local Organizing Committees in fund raising and in contacting Societies to arrange joint meetings.

Dr. Ken. Marshal indicated that he has enjoyed the symposia at the meeting although 5 were too many. Dr. Doug. Jones replied that this was one of the reasons the SPC had reached the 2 per year decision. Having 5 symposia cut into the general session time excessively. Dr. Dick Stein indicated that the symposia were a good idea and were there any plans for more joint meetings? Dr. Tessa Gordon replied that the plan was for a joint meeting with the Canadian Association for Neuroscience in 2001 and the Canadian Pharmacological Society or the American Physiological Society for 2002.

8) CPS Web Site <http://www.physiology.ubc.ca/CPS/Main.htm>

Dr. Alison Buchan reported that the bilingual site is up and running and will be moving to a home with NRC in the near future. Once the site has moved it will remain the responsibility of the Secretary to ensure that the site is regularly up-dated. Dr. Buchan asked that thanks be given to Mrs. Zaira Kahn and Ms. Natalie Gaudreault for their help in creating the site.

There followed additional discussion of the proposed move of Physiology Canada to the web. Dr. Stein suggested that the move be made in time for the next abstracts issue in December 2000. Those members without access to the Internet can contact their Departments and request a print out of the Journal. Dr. Doug Jones suggested that the move be delayed until we know how many individuals/Institutional subscribers will be affected by the change. The following motion was moved “That the editor of Physiology Canada move to publication on the web”.

Motion to approve: Proposed: Dr. C. Cheeseman, Seconded: Dr. W. Cupples  
Carried

9) Results of the Election.

The Vice-President is Dr. Alvin Shrier, Councillors: Drs. E. Chapman and D. Munoz.

10) Other Business

a) CIHR: Dr. Es. Sanders the MRC Regional Director for Alberta gave an update on the progress towards CIHR. Basically the legislation was delayed in the Commons and will not be on line by 1<sup>st</sup> April. It is hoped that the legislation will pass in time to allow CIHR to start in June 2000. The Interim Governing Council has asked the Universities to give a

slate of titles for the new Institutes, this information is available on the CIHR web site:  
<http://www.cihr.org>

The date of the decisions re the final names/number of Institutes has yet to be announced. A call for the names of potential Directors of Institutes has also gone out. Proposals for Consortia are also in the works and funding through the Opportunities programme has been available to interested groups in two competitions. Dr. Shrier commented that there were concerns that the consortia would become members only thus excluding the rest of Canadian scientists. Dr. Sanders replied that this was a risk but that hopefully it would not happen. It would depend in part on the individual Directors of the Institutes.

b) Dr. Doug Jones raised the issue that the Secretary of the Society has a great deal of responsibility both for the Council and AGM meetings as well as the general Winter meeting, however, CPS does not cover the expenses of the Secretary to attend the meeting. He proposed that CPS cover the transportation costs of the Secretary to attend the Winter Meeting.

Motion to approve: Proposed: Dr. D. Jones, Seconded: Dr. Jim Thornhill  
Carried

Dr. Tessa Gordon proposed a vote of thanks to Dr. Jim. Thornhill for organizing the meeting and to the retiring members of Council: Drs Penny Moody-Corbett and Dr. T. Krantis. Dr Gordon then handed the Presidency to Dr. Jim Thornhill who, in turn, thanked Dr. Gordon for all her efforts on behalf of the Society.

The final item was to offer congratulations to Dr. Hugh McLennan this being his 50<sup>th</sup> CPS Winter Meeting.

Meeting adjourned at 6.40pm.



Melville Schachter

**MELVILLE SCHACHTER**

**(1920 - 2000)**

It is my sad duty to report that Dr. Melville Schachter passed away at his home in London, England on the 18<sup>th</sup> of May, 2000 at the age of 79.

Mel Schachter was Head of the Department of Physiology at the University of Alberta from 1965-1985, and was known internationally for his work on the physiology and pharmacology of endogenous vasoactive substances.

Mel was born in Montreal in 1920 and obtained his degrees from McGill University: BSc (Honors Biochemistry) in 1941, MSc (Physiology) in 1942, and MD, CM in 1946. He served in the Royal Canadian Army Medical Corps from 1944-1946. While at McGill he studied with Professor B.P. Babkin, himself a colleague of Professor I.P. Pavlov. Mel therefore always regarded Pavlov as his scientific "grandfather". After graduating, Mel worked as an interne at the Allan Memorial Institute and Royal Victoria Hospital, then as an Assistant Professor of Physiology at Dalhousie University.

Mel left Canada in 1950 and moved to London, England. He worked at the National Institute for Medical Research (1950-1953) and the Lister Institute (1953-1954). Together with co-workers such as Wilhelm Feldberg and Sir William Paton, Mel investigated the release of histamine under a variety of conditions, and the role of anti-histamines. In 1954 Mel joined the Department of Physiology at University College London where he remained until 1965. This was probably one of the most productive and happiest periods of his career, in which he pursued his interests in the field of kinins. This name was proposed, by Mel, for a group of closely related peptides (such as kallidin and bradykinin) which are found in, or produced by, many tissues, for example salivary glands, pancreas, accessory sex glands of the male, wasp venom. Kinins are vasoactive compounds which are of importance in inflammatory conditions. Mel was particularly interested in the possible physiological roles of the kinin-releasing enzymes and the kinins themselves and he published over 100 scientific papers in the field. In 1995, some ten years after his retirement, he was awarded the E.K. Frey - E. Werle Commemorative Medal in recognition of his work on kinins.

Mel left University College London to come to Edmonton as Head of Physiology in 1965. In the twenty years that he was here, he laid the foundation for the department as it is today, and many of the current senior members of the department were appointed by him. Mel brought to the Department of Physiology the culture of research excellence which still marks the department. He was always anxious that the department fulfill its teaching obligations to the very best of its abilities, but he was careful not to overwhelm his academic staff with teaching to the detriment of their research activities. His own preference was for teaching the medical students, especially giving "live" demonstrations to small groups of students. Here he was at his best in conveying enthusiasm and a sense of wonder at results which he was seeing for the umpteenth time but which were completely new to the students.

PHYSIOLOGY CANADA

Following his retirement in 1985 Mel, a confirmed anglophile, returned to England with his wife Ruth. There he continued his work in an honorary capacity at University College London and, subsequently, in the Department of Pharmacology at King's College London.

Mel was often at odds with the University establishment over administrative matters, but those of us that knew him well knew that he was a man of extraordinary sensitivity and kindness, particularly towards those less-privileged among us. He was at his happiest when around children and young people, and many of us remember fondly his family barbeques here in Edmonton.

Mel Schachter will be remembered as a major influence in the lives of many of us who grew up as Faculty members in his department. He will be very much missed.

Dr. Esmond J. Sanders  
Professor and Chair  
Department of Physiology  
Faculty of Medicine and Dentistry  
University of Alberta

Volume 31, Number 1, June, 2000

**23rd SARRAZIN LECTURE**

by

James P. Lund

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## REVELLING IN THE JOYS OF MASTICATION

### Introduction

I was lucky to grow up in South Australia at a time when teenagers worried little about their economic future. When I was 18, and finishing High School, I thought that I would enrol in a general science program at the "Uni" the next year. However, my girlfriend decided to do Medicine, so I thought that I would do the same. Then I found out that this would take one third of my life to that point (6 years), so I opted for Dentistry. This gave me the advantage of taking most of my courses with the medical students in the first three years, and also saved a year from the rest of my life. Three weeks after classes started, my girlfriend dumped me.

I graduated in 1966, and went to a country town, Mt Gambier, to do a little Dentistry, and play Australian football on the weekends. "Footy" and Dentistry are not very compatible, and I would often go into the clinic on Mondays with my fingers in bandages. Therefore, I decided to train as an Oral and Maxillofacial Surgeon, because bone surgeons need strength, not finesse. Like most young Australians, I wanted to go abroad for a few years, so I decided to do this overseas.

Peter Dellow had been a Lecturer in Physiology at the University of Adelaide. About the time that I graduated, he had accepted a position at The University of Western Ontario, so I wrote to him to ask if he knew of any good programs in Oral Surgery in Canada. "No" he wrote back, "but why not do a Ph.D in Physiology?" I agreed, not realising that Surgeons get paid well for staying up late working on warm mammalian bodies, while Physiologists do not.

The Physiology Department at Western was run by Professor J.A.F. Stevenson, Jim to his friends, Jafs to the Grad. Students. Long before Twiggy, the rise of the Super Models, the Granola Generation and Health Food Consciousness, JAFs and many researchers in the Department worried about diet. Control of Food and Water intake was the main research theme, and the most common research outcomes were urinary volume, faecal weight and roughage content. I was made head keeper of a colony of hyperphagic rats, weighing in at about 1 kg each, that Miss Blanche Box, Professor Stevenson's technician, had kindly prepared for Peter Dellow. It was thought that their salivary glands might hypertrophy- a not unreasonable assumption for animals that would consume their own weight in wood chips if pencils were pushed into their cages.

However, a few months of spit measurement and uro-copric research convinced me that my future did not lie in secretory side of the digestive process, so I switched to the intake end of the alimentary canal, and began to study the control of mastication.

### **The Rabbit as a Chewing Machine** (with apologies to Sir John Eccles).

I decided to find out how the complex rhythmic movements that we use to chew up our food are produced by the brain. In 1961, Bullock had written that the mechanism by which patterned motor activity is produced by the nervous system is "one of the core questions of general neurology". At the time that he was writing, the prevailing concept was that alternating activity in different groups of muscles during rhythmic movements like mastication and locomotion resulted from switching between reciprocal reflexes. Sherrington (1917) had been one of the first to propose this. He pointed out that biting

into food stimulates the Jaw Opening Reflex. This stretches the spindle receptors in the muscles that close the jaw, leading to the Jaw Jerk (Closing) Reflex. The two reflexes tend to alternate "so long as there is something biteable between the jaws".

We chose to use the anaesthetised rabbit for these experiments because rhythmical mastication is easily induced in this preparation by repetitive stimulation of the sensorimotor cortex, and the corticobulbar tracts. We used neurograms to record the output of motoneurons, and were able to show that the pattern of alternating bursts in Jaw Opener and Jaw Closer motor nerves remained after decerebration and paralysis ("fictive" mastication). To prove that this rhythmic pattern was intrinsic to the brainstem, we cut the spinal cord and the cranial nerves and turned off the respirator while we stimulated the corticobulbar axons with a random train of shocks. Finally, I did a cross-correlation analysis by hand to show that the masticatory rhythm was not linked to the heartbeat. In those days, most data handling was done manually. The paper was published in the *Journal of Physiology* in 1971 at about the same time as I received my Ph.D. and left for Montreal.

### **The Primate Years**

I decided to spend a couple of years as a postdoc with Yves Lamarre, a young Neurophysiologist who had recently returned to the Université de Montréal after his own postdoctoral studies with Poggio at John's Hopkins, Fessard in Paris and Granit in Stockholm. When I arrived, Professor J-P Cordeau, headed the department. He had persuaded Professor Herbert Jasper to leave the MNI and to found with him the first MRC Group in 1966. The Département de physiologie de l'Université de Montréal was clearly the one-stop shop for all revealed wisdom in neurophysiology.

Another attraction was that Yves had rhythm. Yves and his students were working on the tremor associated with Parkinsonism, using an adaptation of the monkey model that had been developed by Louis Poirier, and cerebellar tremor in cats under harmaline. His graduate students included Bruce Jacks, a wonderful indépendantiste from Vancouver, who unfortunately died young, and Claude De Montigny, who went on to a great career in Psychiatric research. I participated in some of these studies, and with Yves' help, was able to set up my own experiments to describe the patterns of neural activity in the motor cortex of awake monkeys while they ate various foods.

Although I had planned to spend only a couple of years in Montreal, doing some neuroscience and learning a little French, I got a job offer from the Faculté de médecine dentaire that allowed me to much more time for research than I could ever hope for in Adelaide. I was given a lab. in the Département de physiologie and continued to collaborate with Yves and also with Ernie Puil, who had arrived from Vancouver via France to work with Herbert Jasper.

At about this time, Yves and I did several series of human experiments. Among other things, we found that cutting out the feedback from periodontal pressoreceptors by anaesthetising the teeth reduced biting force. This was curious, because if the same receptors were stimulated by tapping on the teeth, the jaw closing muscles were inhibited, not excited. This was some of the first evidence that a sensory input can have opposite effects on motoneurons, and that the outcome depends on the sort of movement we are making.

In 1976, I became a member of the MRC Group that was now headed by Yves. The other members were Jacques Courville, an excellent Neuroanatomist who worked

mainly on the cerebellum, Serge Rossignol (Comme les skis!), and Allan Smith, a Trifleuvien who had been sent to Switzerland for a little finishing. Allan and I decided to exploit the fact that when you work on the jaw motor system, it is relatively easy to record from its motoneurons in the brainstem during chewing and biting, a thing that is very difficult to do in the spinal cord during locomotion. At the time, there was a lot of interest in the idea that " motoneurons may be controlled via the spindle loop during voluntary movement (follow-up servo-control). According to this model, the first step in the initiation of movement was the excitation of ( motoneurons. This would cause intrafusal fibres to contract, which excited spindle afferents and finally " motoneurons. However, we found that, although ( motoneurons started to fire at least as early as small " motoneurons during voluntary biting, this did not lead to significant spindle feedback until later in the task. Barry Sessle from the U of T, and my first Post-doctoral Fellow, Toshiki Murakami from Niigata, also worked on these experiments.

### **Rabbit Redux**

Like John Updike, I returned to the rabbit as an allegory of the human condition (or the condition of some humans). With the help of several collaborators, including Serge, Trevor Drew, Kwabena Appenteng, Jérôme Séguin, and Gilles Lavigne, I was able to show that the Jaw Opening Reflex, the equivalent of the Flexion-Withdrawal Reflex in the limbs, was modulated during mastication in ways that seemed to reflect the needs of this system. First, we found that the reflex response during mastication depended on the type of afferent input: large fibre input was tonically suppressed, while responses to small fibres, including nociceptors, went up during the Jaw Closing phase of mastication. We concluded that the central pattern generator (CPG) was inhibiting mechanoreceptor input to stop disruptions of the movement pattern by innocuous sensory feedback, while heightening protection against self-injury (e.g. biting the tongue). Later, we showed that the reflex response to stimulating the periodontal pressoreceptors becomes excitatory to the jaw closing muscles during mastication in rabbits, just as it does during voluntary biting in humans.

With Kurt Olsson and K-G Westberg from Umeå and Revers Donga from London, I began to study brain-stem interneurons that received sensory inputs from the mouth, teeth and jaw muscles, and we described the way in which they were modulated during fictive mastication. At the time, models of motor systems usually separated the CPG and the reflex circuits that were supposed to be under their control. However, it gradually became clear to us that there was no clear separation between the two. Almost every brain-stem neurone that is active during fictive mastication responds to some sort of peripheral input, and there really is no functional boundary between the CPG and sensory inputs. What we did find however, was that the CPG was not a unitary structure: neurones that were active during one type of mastication (e.g., chewing on the right molar teeth) were often inactive during another pattern.

The difficulty of separating sensory inputs from the CPG surfaced again when Arlette Kolta, Serge Rossignol, K-G. Westberg and I looked at the behaviour of trigeminal muscle spindle afferents. We found that central axon of the afferent seems to function as a last-order interneurone for the CPG during fictive mastication. At the same time, communication between the central axon and the rest of the neurone is cut off, perhaps by axo-axonic synapses controlled by other neurones of the CPG. This was the first time that a phenomenon like this has been uncovered in mammals.

### **Administration, Pain, and Dysfunction**

A large part of my life during the last 15 years has been spent on clinical research, and on that most applied of the Psychosocial Sciences, University Administration. I will describe this last facet of my career very briefly, since it will be of little interest to the readership of Physiology Canada. However, pain always breaks through our indifference, since few of us can ever avoid at least one prolonged bout of pain during our lives. Unfortunately, most chronic pain has no clear aetiology, nor a specific cure, despite what Chiropractors, and some Dentists and Orthopaedic Surgeons would have us think. One of the most prevalent assumptions is that many common forms of chronic muscle pain, such as fibromyalgia, lower back pain, 'tension' headaches and temporomandibular disorders, are caused by hyperactivity in the muscles, and that pain itself maintains hyperactivity (The Vicious Cycle Hypothesis of Travell). Charles Widmer from the University of Florida, Christian Stohler from Ann Arbor and I studied the relationship between pain and motor activity, and found little evidence in the literature to support the Vicious Cycle concept. We came up with another way of looking at the relationship between chronic pain and motor dysfunction that we have called the Pain-Adaptation Model. We tested this model using hypertonic saline injections to stimulate muscle nociceptors in human volunteers and in rabbit preparations. We have been able to confirm that motor systems adapt to the presence of pain in ways that seem to promote healing, or at least that reduce reinjury. These adaptations include the slowing of rhythmic motor cycles by a direct effect on the CPG, an inhibition of agonist muscle bursts and activation of antagonists. Together, these effects slow movement and reduce force output.

I have also participated in several clinical trials on chronic pain and on the rehabilitation of dental patients using endosseous implants to support prostheses. The clinical research group that I helped to create in Montreal is now headed by my wife and fellow professor at McGill, Dr Jocelyne Feine.

### **Comparative Theology**

Like so many ageing Physiologists, I seem destined to return to religion in the twilight of my career. After all, it happened to Sir John Eccles, and he won a Nobel Prize. Rather than fight this trend, I have decided to reactivate a research theme that I had begun to explore as a graduate student- Comparative Theology. Like so many enthusiastic young scientists, I was crushed by rejection, specifically by a letter refusing to publish a manuscript that I and my co-author had submitted to the Journal of Irreproducible Results just before Christmas, 1971. We abandoned the field.

Although still hesitant, I now feel confident enough to finally present our pioneering work in this field for the consideration of the members of this Learned Society. I am sorry that my co-author did not survive the shock of rejection to see this day. He always suspected that the referees had been tainted by Liberation Theology.

The Lateral Hypothalamus: Seat of the Soul

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\* The authors wish to thank Brother William  
for the illuminations and Sister Beatrice  
for the illustrative tapestry.

Introduction

It has been reported by Montemurro & Stevenson (1957) that rats with lesions of the lateral hypothalamus pine away and die. The traditional explanation of this phenomenon has been that the lesions destroy areas associated with the regulation of eating and drinking. However, more probable explanation, in the opinion of the authors, is that the lesions destroy the immortal soul or allow it to escape through the electrode holes.

Methods

Twenty good Catholic male rats, chosen for their good demeanour and clean appearance were housed in individual cages, receiving food and water daily during the hour following matins. They were taught to make the sign of the cross with their right forepaw. Positive reinforcement consisted of small sips of sacramental wine.

Under incense anaesthesia, all animals were tonsured and cannulae were bilaterally directed into the lateral hypothalamus by blind faith. Ten animals were lesioned by dropping pellets of fire and brimstone into the bottom of the tubes. The operated controls were treated instead with 1 cc of Holy Water.

At the termination of the study, animals were killed by a blow with a silver candlestick: their brains were exorcised and fixed with Frankincense. Sections of the brain were cut at 50 millicubits and mounted on stained glass.

Control animals were buried behind the north cloisters while the lesioned animals were cremated and their ashes scattered along the Ulster border. The laboratory was finally reconsecrated.

### Results

Upon recovery, the operated animals would no longer make the sign of the cross, drink wine or eat sacramental wafers, even when the latter were proffered by My Lord the Bishop. The control animals, however, responded as before and were overjoyed to see His Grace, who kindly addressed them on the subject of papal infallibility.

### Discussion

Similar symptoms to those seen in our operated group have been reported by Torquemada (1490) and O'Hea (1968) in Protestants. If the present results were directly applicable to humans, it would seem that the commonly held opinion that Mr. Ian Paisley has holes in his head might be based on more than superstitious beliefs.

It is probable that the stress placed on the human organism by wild, fundamentalist preaching and hymn singing causes small areas of haemorrhage and eventual necrosis in these vital hypothalamic regions.

In conclusion, it would appear that the soul, which resides in the lateral hypothalamus, can be destroyed by lesions of both chemical and theological origin.

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**ABSTRACTS OF RECENT PH.D. THESES**

- Title: Functional Maturation of Phrenic Motoneuron Electrical Properties and Diaphragm Contractile Properties During Perinatal Development in the Rat
- Author: Miguel Martin-Caraballo
- Supervisor: John J. Greer, Department of Physiology, Division of Neuroscience, University of Alberta
- Current: Postdoctoral studies at the University of Texas at Houston, with Dr. Stuart Dryer

There is a critical period at approximately embryonic day (E)17 during which phrenic motoneurons (PMNs) undergo a number of pivotal developmental events including the inception of functional recruitment via synaptic drive from medullary respiratory centres, contact with spinal afferent terminals, the completion of diaphragm innervation and a major transformation of PMN morphology. The objective of this thesis was to test the general hypothesis that there would be a marked maturation of PMN electrophysiological and diaphragm contractile properties occurring in conjunction with these developmental processes. PMN properties were measured via whole-cell patch recording utilizing a cervical slice-phrenic nerve preparation isolated from perinatal rats. Muscle force recordings and intracellular recordings of endplate potentials were measured using phrenic nerve-diaphragm muscle *in vitro* preparations isolated from rats on E18 and postnatal day (P) 0-1.

*Development of PMN electrophysiological properties:* From E16 to P1, PMN property changes included the following: i) 10 mV hyperpolarization of the resting membrane potential, ii) three-fold reduction in the input resistance, iii) 12 mV increase in amplitude and 50% decrease duration of action potential, iv) major changes in the shapes of afterpotentials, v) increases in rheobase current and steady state firing rates. Electrical coupling between PMNs was detected in 15-25% of recording at all ages studied.

*Development of  $K^+$  conductances:* PMNs expressed outward rectifier ( $I_{KV}$ ) and A-type  $K^+$  currents that regulated action potential and repetitive firing properties throughout the perinatal period. There was an age-dependent leftward shift in the activation voltage and a decrease in the time to peak of  $I_{KV}$  during the period from E16 through to birth. The most dramatic change during the perinatal period was the increase in the  $CA^{++}$ -dependent 'hump-like' ADP and mAHP, respectively.

*Development of diaphragm contractile properties:* The following age-dependent changes occurred between ages E18 and P1: i) twitch contraction and half-relaxation times decreased ~2- and 3-fold, respectively, ii) maximal tetanic force levels increased ~5-fold, iii) the range of forces generated by the diaphragm in response to graded nerve stimulation increased ~2.3-fold, iv) the force-frequency curve was shifted to the right, and vi) the propensity for neuromuscular transmission failure decreased. In conclusion, the diaphragm contractile and PMN repetitive firing properties develop in concert so that

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the full-range of potential diaphragm force recruitment can be utilized and problems associated with diaphragm fatigue are minimized.

Title: Prenatal Development of the Rat Phrenic Nerve and Diaphragm: Basic Embryology, Role of Psa-ncam and the Pathogenesis of Congenital Diaphragmatic Hernia

Author: Douglas Watt Allan

Supervisor: John J. Greer, Department of Physiology, Division of Neuroscience, University of Alberta

Current: Postdoctoral studies at Harvard with Dr. Sefan Thor

The phrenic nerve and diaphragm constitute the major neuromuscular system of the respiratory network, and its proper development is critical for survival at birth. However, data regarding the prenatal development of the phrenic nerve and diaphragm are inconsistent and incomplete. Studies performed here have: 1) Described the embryogenesis of the phrenic nerve and diaphragm and the maturation of phrenic motoneuron morphology throughout prenatal development; 2) Examined the molecular control of certain aspects of phrenic-diaphragm morphogenesis; 3) Performed parallel studies investigating the pathogenesis of congenital diaphragmatic hernia in a rodent model of this developmental anomaly.

These studies identify the primordial diaphragm (the pleuroperitoneal fold) and describe phrenic axon outgrowth and the formation of the diaphragm neuromusculature from the time of initial axonal outgrowth (E11) to birth in the rat. This offers substantive understanding of phrenic-diaphragm development and demonstrates that many textbook descriptions are likely incorrect. These studies have also found that expression of the anti-adhesive polysialylated (PSA) form of neural cell adhesion molecule (NCAM) implicates its role in selective guidance of phrenic axons as they diverge from brachial axons at the brachial plexus. A whole embryo culture system has been adopted for future testing of this hypothesis. PSA-NCAM has also been found to be a potential modulator of myotube membranes of separating myotubes and evidence suggests that its enzymatic removal inhibits myotube separation in the rat diaphragm. Retrograde labeling with the lipophilic dye, DiI, of phrenic motoneurons which analysed somatodendritic morphology throughout embryonic development showed that major morphological reorganisation and maturation occurs subsequent to the onset of functional respiratory drive, implicating this drive in these modifications.

Congenital diaphragmatic hernia (CDH) is an often fatal developmental disorder in which a large region of the diaphragm is missing. How it arises embryologically is poorly understood. Using a well-established nitrofen-induced rodent model of CDH, we have performed the first systematic assessment of prevalent hypotheses regarding CDH pathogenesis. Results indicate that these theories are incorrect and refocus the field to an examination of early developmental events during formation of the pleuroperitoneal fold.

Title: P<sub>1</sub> Purinoceptor Neuromodulation in the Transduction of Myocardial Ischemia by Nodose Ganglion Cardiac Afferent Neurons

Author: Gregory W. Thompson

Supervisor: Drew Armour, Department of Physiology & Biophysics, Dalhousie Univ.

Current: Studying Medicine at Dalhousie

Nodose ganglion cardiac afferent neurons transduce sensory information from the heart to central neurons. The function of these afferent neurons during myocardial ischemia and the role that purinergic and peptidergic agents play in transducing myocardial ischemia have not been investigated. The effects of chemical (adenosine receptor agonists and antagonists, bradykinin, and substance P) and ischemic stimuli on the epicardial sensory endings of porcine nodose ganglion cardiac afferent neurons were studied *in situ* using an extracellular recording technique. Intramyocardial injections of fluorescent neuronal tracers retrogradely labeled perikarya in nodose ganglia and the ventrolateral nucleus ambiguus, anatomically confirming cardiac vagal afferent pathways to the central nervous system. Epicardial application of specific adenosine A<sub>1</sub> and A<sub>2</sub> receptor agonists, the peptides bradykinin and substance P, as well as transient (30-90 seconds) coronary artery occlusion modified the spontaneous activity generated by the majority of afferent neurons tested. The majority of ischemia-sensitive afferent neurons were also sensitive to P<sub>1</sub>-purinergic and peptidergic agonists. Furthermore, responses to peptides paralleled those induced by ischemia. P<sub>1</sub>-purinergic antagonists not only blocked responses induced by adenosine receptor agonists, but also blocked responses induced by ischemia or peptides. Taken together, these data indicate that: 1) neuroactive agents released during ischemia modify the activity generated by nodose ganglion cardiac afferent neurons, and 2) adenosine receptor antagonists are capable of attenuating afferent neuronal responses not only to myocardial ischemia, but also to peptides. These data demonstrate that adenosine receptor mechanisms are involved in the transduction of myocardial ischemia, including the modulatory role of peptides known to be liberated during myocardial ischemia. Targeted pharmacological strategies may be developed for the management of ischemia-induced reflexes, including cardiac nociception.

Title: The Relative Potency of Testosterone and Dihydrotestosterone in the Rat Ventral Prostate: Role of 5 $\alpha$ -reductase

Author: A. Stuart Wright

Supervisor: Roger Rittmaster, Department of Physiology & Biophysics, Dalhousie Univ.

Current: Postdoctoral studies at Oregon Health Sciences University, Portland

Testosterone (T), the major circulating androgen, must be converted to dihydrotestosterone (DHT) by the enzyme 5 $\alpha$ -reductase (5 $\alpha$ -R) for maximal activity in the prostate. Based on its higher affinity for the androgen receptor, its high intraprostatic concentration and the observation that men with congenital 5 $\alpha$ -R deficiency have small prostates, DHT was considered to be the only active androgen in the prostate. In both rats and men, administration of 5 $\alpha$ -R inhibitors such as finasteride results in prostate shrinkage but not to the same extent as castration. The most probable reason is the reciprocal rise in intraprostatic T that accompanies the decrease in DHT on 5 $\alpha$ -R inhibition. The objective of the studies presented here was to investigate the relative potencies of T and DHT in prevention of rat ventral prostate regression and in regrowth.

To determine the relative potencies of intraprostatic T and DHT in preventing regression, castrated rats were implanted for 4 days with varying sizes of T pellets in the presence or absence of finasteride treatment. In the absence of finasteride, virtually all intraprostatic T was converted to DHT, creating a dose-response for DHT effects in the prostate. In the presence of finasteride, DHT was suppressed to the levels found in a castrated rat and a dose-response for T effects was achieved. Prostate regression consists of atrophy through reduced secretory activity and cell loss through apoptosis. DHT was 2.4 times more potent than T in maintaining normal prostate weight and lumen mass, a measure of epithelial cell function. However, intraprostatic T and DHT were able to inhibit apoptosis with equal potency, indicating that 5 $\alpha$ -R inhibition in an intact animal results in atrophy and minimal apoptosis because of the potency of intraprostatic T.

In order to examine the relative potencies of T and DHT on prostate growth, rats were castrated for 2 weeks to allow the prostate to fully regress and were given T implants in the presence or absence of finasteride to create dose-responses for the effects of intraprostatic T and DHT, respectively. 1.6-1.9 times more T than DHT was needed to achieve half-maximal responses in markers of hypertrophy and hyperplasia and a 2 - 3 fold higher threshold was observed for T compared to DHT before significant growth occurred. A more pronounced potency difference was found when the relationship between serum T levels and prostate growth examined. 11-16 times more serum T was required for half-maximal prostate growth when DHT formation was blocked by finasteride, suggesting that 5 $\alpha$ -R plays a role in prostatic androgen accumulation. Whether T or DHT pellets were used to provide the circulating androgen, the concentration of DHT in the ventral prostate in the absence of finasteride was identical, indicating that in terms of prostate physiology, DHT could serve as the major circulating androgen. However, to achieve similar levels of T or DHT in serum, much larger DHT pellets were needed, consistent with the known rapid metabolism of DHT in tissues other

than the prostate.

Collectively, these results indicate that the role of 5 $\alpha$ -R in the prostate is two-fold: it converts T to a moderately more potent androgen and permits the accumulation of androgen at low serum T concentrations. T has probably arisen as the major circulating androgen instead of DHT because it can be aromatized to estradiol, which has important roles in male physiology.

Title: Contributions of GABA to Reorganization in Raccoon Primary Somatosensory Cortex.

Author: Liisa Tremere

Supervisor: Douglas Rasmusson, Department of Physiology & Biophysics, Dalhousie University

Current: Postdoctoral studies at Dalhousie with Steve Barnes

In the adult raccoon, neurons in somatosensory cortex acquire new receptive fields (RF) during denervation-induced reorganization. Furthermore, RF size changes considerably during reorganization. Intra-cortical inhibition has been shown to regulate the RFs of cortical neurons in the normal cat and primate. The central question of the present thesis was whether intra-cortical inhibition could account for differences between control neurons and neurons studied at different stages of reorganization. To examine this possibility, bicuculline methiodide (BMI), a specific antagonist of the GABA<sub>A</sub> receptor was applied to cortical neurons in 12 normal raccoons and 10 raccoons that had previously undergone amputation of the fourth forepaw digit 2 weeks to 37 weeks earlier. BMI application altered the receptive fields in 62/102 neurons in the control animals and 64/103 neurons in denervated cortex. In reorganized cortex, simple receptive field expansion that preserved the shape of the original receptive field was seen in 39 neurons. In 22 cells BMI application produced more complex changes such as a transition from single digit to multi-digit fields, a degree of expansion that was never produced in the normal animal. These data indicate that pre-existing anatomical connections cannot account for the appearance of new RFs after amputation and suggest that cortical inhibitory synapses shape or focus the RF in the normal cortex as well as during reorganization.

Title: Molecular Mechanisms Contributing to the Expression of Utrophin at the Mammalian Neuromuscular Synapse.

Author: Anthony O. Gramolini

Supervisor: Bernard Jasmin, Dept. of Cellular & Molecular Medicine, University of Ottawa.

Current: Post-doctoral work at the Howard Hughes Medical Institute, Duke University, North Carolina with Dr. Vann Bennett

Duchenne muscular dystrophy (DMD) is the most severe and prevalent primary myopathy. This disease is characterized by repeated cycles of muscle fiber degeneration and regeneration with an eventual failure to regenerate leading to the progressive replacement of myofibers by adipose and connective tissues. The genetic defects responsible for DMD are mutations in the short arm of the X chromosome which prevent the production of normal size dystrophin, a large cytoskeletal protein of 427 kDa. In 1989, Love and colleagues showed the existence of a gene on chromosome 6q24 that encodes a cytoskeletal protein, called utrophin, which displays a high degree of sequence similarity with dystrophin (Love, D.R., Hill, D.F., Dickson, G., Spurr, N.K., Byth, B.C., Marsden, R.F., Walsh, F.S., Edwards, Y.H. and Davies, K.E. (1989) An autosomal transcript in skeletal muscle with homology to dystrophin. *Nature* **339**, 55-58). However, in contrast to the homogeneous distribution of dystrophin along muscle fibers, utrophin preferentially accumulates at the neuromuscular junction. Due to this sequence similarity between dystrophin and utrophin, it has been suggested that increased expression of utrophin into extrasynaptic regions of dystrophic muscle fibers may represent an alternate therapeutic strategy for DMD. Recently, it has been confirmed that the upregulation of utrophin can, indeed, functionally compensate for the lack of dystrophin and alleviate the muscle pathology. In this context, it thus becomes essential to determine the cellular and molecular mechanisms presiding over utrophin expression in attempts to overexpress the endogenous gene product throughout skeletal muscle fibers.

In this Thesis, I explore the mechanisms underlying the selective accumulation of utrophin at the postsynaptic membrane of the neuromuscular synapse. We determined by *in situ* hybridization that local transcription contributes to the accumulation of utrophin at the neuromuscular junction. Using direct injections of utrophin promoter-reporter constructs into skeletal muscle, we also defined the promoter elements involved in this local transcription and determined that the N-box element is a key consensus sequence that directs transcriptional control of utrophin expression at the neuromuscular junction. Furthermore, additional experiments revealed that utrophin gene transcription is dependent on the extracellular matrix proteins agrin and ARIA/herregulin, and this regulation is dependent upon the N-box element. Indeed, *in vitro* transfection assays and electromobility shift assays indicated that agrin and ARIA/herregulin may ultimately initiate a cell signaling cascade that activates the ETS-related transcription factor, GABP which binds and activates the N-box element. In a separate series of studies, we also examined the effect of myogenesis in culture on the transcriptional regulation of utrophin gene expression. In these experiments, we

determined by RT-PCR, immunoblotting, and nuclear run on assays that, in contrast to the large changes in AChR, utrophin expression was only marginally increased under these conditions.

In addition to these transcriptional events that control the levels and localization of utrophin, it also became apparent that transcription alone could not account for the complete regulation of utrophin expression under certain conditions. Indeed, we observed a discordant relationship between utrophin transcript levels and protein levels in regenerating muscles or muscles obtained from DMD patients, indicating that utrophin expression may be controlled by post-transcriptional events. Altogether, it appears likely that the regulation of utrophin levels and localization are coordinately regulated both by transcriptional and post-transcriptional events, ultimately leading to the preferential accumulation of utrophin at the neuromuscular junction.

Together, these observations are therefore relevant for our basic understanding of the events involved in the assembly and maintenance of the postsynaptic membrane domain of the neuromuscular junction and for the potential use of utrophin as a therapeutic strategy to counteract the effects of DMD.

**F.C. MacIntosh Senior Visiting Professorship  
of the Canadian Physiological Society**

Each year the Canadian Physiological Society offers a Senior Visiting Professorship to an outstanding senior Canadian physiologist. This senior Visiting Professorship is named after Dr. F.C. (Hank) MacIntosh and is sponsored by the Corporate Patrons of the Canadian Physiological Society. The purpose of the Visiting Professorship is to promote collaboration and exchange between physiology departments and investigators at Canadian universities. The Visiting Professor is to be encouraged to visit two or more departments within the same region of the country so nominations can come from a single department or jointly from two or more. The Visiting Professor would be expected to spend several days at each institution giving seminars, meeting with other investigators and holding sessions with the department's graduate students.

The selection of the senior Visiting Professor will be the responsibility of the Council of the Canadian Physiological Society and will be based upon the scientific achievements of the candidates. Nominees for this award should be members of the Canadian Physiological Society and have made a contribution to the Society. Normally the Visiting Professorship will not be awarded to candidates before the tenth year from receiving their highest degree.

Nominations should be sent to the Secretary of the Society at the address given below. Each nomination must include a letter from the sponsor/s setting out the proposed itinerary, and a curriculum vitae of the candidate.

Individuals who wish to be considered for the F.C. MacIntosh Visiting Professorship are encouraged to approach departments for sponsorship, but they cannot apply directly. Letters of nomination and supporting documents should be sent to:

Dr. Alison M.J. Buchan, Secretary CPS  
Department of Physiology,  
University of British Columbia,  
2146 Health Sciences Mall, Vancouver, B.C., V6T 1Z3  
Telephone (604) 822-2083 Fax (604) 822-4727  
e-mail: **buchan@cs.ubc.ca**

**J.A.F. Stevenson Visiting Professorship of the  
Canadian Physiological Society**

Each year the Canadian Physiological Society offers a Visiting Professorship to an outstanding young Canadian physiologist. The purpose of the Visiting Professorship is to promote collaboration and exchange of information among investigators at Canadian universities and to strengthen graduate training programs in physiological research.

The Society will provide travel expenses for the Visiting Professor; living expenses will be the responsibility of the host department. Nominations for the award are to be made normally by the Chair of the host department of physiology to enable a distinguished young investigator from another Canadian institution to spend two to seven days at the host department giving lectures and graduate seminars. The host department of physiology can be any one of the sixteen in Canadian university faculties of medicine.

The candidate chosen to receive the Visiting Professorship will also present a lecture at the Annual Winter meeting of the Society. Partial reimbursement of expenses to attend the Annual Winter Meeting will be the responsibility of the Canadian Physiological Society.

The selection of the Visiting Professor will be the responsibility of the Council of the Canadian Physiological Society and will be based on the scientific achievements of the candidate. Nominees for this award should be a member of the Canadian Physiological Society and in good standing for at least one year and should have contributed to the Society. Normally, the Visiting Professorship will not be awarded to candidates after the tenth year from receiving their highest degree. In the event that more than one host University has requested the chosen recipient, the University which first placed the request will be given preference.

Nominations should be sent to the Secretary of the Society at the address given below. Each nomination should include a letter from the sponsor setting out the proposed itinerary and include the curriculum vitae of the candidate.

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