

PATHWAYS EXPANDED ARTICLE: Spring 2015

Research News

Forty Years of Devoted Research

By John L. Semple

After 40 years of intelligent and devoted research in the field of lymphatic circulation Dr. Miles Johnston is retiring from his position as a Senior Scientist in the Brain Sciences Program at the Sunnybrook Research Institute and a Professor in the Department of Laboratory Medicine and Pathobiology, University of Toronto.

The first time I met Miles Johnston was in 1983, everyone was crowding into his office in the Medical Science Building at the University of Toronto having a look at one of the first Macintosh Apple desktop computers that anyone had seen. He was demonstrating how he could plot his data on a graph just by feeding in the numbers. We were all amazed. At that time he was only several years after returning from his post-doctoral training at the Babraham Institute, Cambridge, England from 1979-1981. He returned to Canada to take up a faculty position at the University of Toronto. Currently, he is a Professor in the Department of Laboratory Medicine and Pathobiology and is a Senior Scientist in the Brain Sciences Program at the Sunnybrook Research Institute. Dr. Johnston's work focuses on the lymphatic circulation and its role in the drainage of cerebrospinal fluid.

He started his career here in Toronto where he received a B.Sc. (1974) in Physiology/Pharmacology at the University of Toronto and a Ph.D. in the Division of Experimental Pathology (Department of Pathology) at the same Institution in 1979. Following post-doctoral training at the Babraham Institute, Cambridge, England from 1979-1981, he returned to Canada to take up a faculty position at the University of Toronto.

Rather than write a tribute type of article on Miles I decided to ask specific questions about his career. Questions that might give readers some insight into choices he had, decisions he made as well as high points in his career of research in lymphatic physiological science. The following are the questions I presented to Miles and his answers:

What were your key influences (role models) in choosing this career?

I can say without hesitation, that I never had any ambition to be a professor. I stumbled into this career quite by chance. I remember sitting outside the Sidney Smith Building on St. George Street as I was now finished with my 4th year final exams at the University of Toronto and my next move was unclear. One of my classmates happened to pass by and told me that he had applied to Graduate School and in passing, gave me a copy of the School of Graduate Studies handbook. On leafing through this, I came across the Department of Pathology. This seemed strange to me at the time as this was a clinical Department and it was not clear how a non-MD would fit it. As I had nothing better to do, I walked over to the Medical Sciences Building and took the elevator to the 6th floor. On attempting to find the graduate office I came across an elderly gentleman (as I would find out later he was 50 years old at that time!), and he was kind enough to talk to me about opportunities in Pathology for an MSc or PhD degree. This 'gentleman' was Dr. Henry Movat and he was one of the world authorities on the inflammatory response. One thing led to another and he accepted me into his lab as a graduate student.

Graduate school was entirely different from anything I had experienced before. My supervisor Dr. Movat was an amazing man and others in the Department of Pathology, most notably Dr. Hay and Dr. Ranadive were very helpful and supportive of my efforts. Dr. Jack Hay was an especially important mentor for me. He introduced me to the lymphatic system and I have enjoyed his company and sage advice enormously over the years. I owe him a great deal as he has had a significant impact on my life.

In 1979, we moved to England to pursue post-doctoral studies at the Babraham Institute in Cambridge under the guidance of Dr. John Gordon. Our time in Cambridge was very enjoyable, in part due to the great academic atmosphere and in part due to our immersion in a new culture. Dr. Gordon's support no doubt helped pave the way for my successful application to the MRC for a Scholarship award.

What type of support did you get to pursue this direction?

I was very lucky to receive MRC funding to support my PhD training, post-doctoral studies in England and my earlier career (MRC Scholarship award, which paid me for 5 years at the Assistant Professor level). If I had not received the latter, my research career would have ended since the University of Toronto was not hiring new faculty in the early 1980's. After a 5-year period when the Scholarship expired, the University of Toronto and Sunnybrook Hospital supported me until retirement. I should also note that I was very lucky to receive MRC/CIHR grants, which funded my research for most of my career.

Why did you pursue a career focusing on the physiology of lymphatics and lymph nodes?

Undoubtedly, Dr. Jack Hay was the most important influence in my choice of lymphatics as a research topic. He introduced me to the lymphatic circulation as part of my inflammation studies as a graduate student. At that time, we were collecting lymph as a way to access chemical mediators from inflammatory sites. However, a research experiment in England during my post-doctoral studies, cemented my interest in this area. Another student in Dr. Gordon's lab (Dr. Bill Martin) was studying pharmacological issues related to vascular smooth muscle. He suspended rings of aortic tissue in an organ bath and quantified the contractile responses of the tissue segments. On one occasion he allowed me to set a ring of sheep intestinal lymphatic into his system and test whether it would respond to a thromboxane analogue. We had no expectation that anything would happen but remarkably, the lymphatic started contracting rhythmically and with great force. This was very exciting at that time and ultimately, studies of lymphatic contractile activity would provide the foundation for my early academic career.

Can you give us your definition of "collaboration" in research? Why do you think this is important?

No one person can have the expertise to run a complex research program. In a modern lab, many disciplines (clinical, physiological, molecular, statistical etc) are required for a successful project. The positive outcome of my research studies is due in no small part, to the talented collaborators that I have had the privilege to work with.

What individuals both local and international stand out as colleagues and collaborators?

Apart from those already mentioned (Dr. Henry Movat and Dr. Jack Hay) there are several others who stand out as having made very important contributions to my work and career.

Dr. Bill Nelson played a vital role in setting up the Trauma Program at Sunnybrook Hospital and he was instrumental in introducing me to the Sunnybrook community. In addition, he paved the way for my move to Sunnybrook and facilitated their financial support for my career. I can say without hesitation that without his friendship and support, my academic career would never have progressed.

Dr. Michael Flessner taught me how to apply mathematics to a study of physiological issues. We worked together to design the experiments that demonstrated an important role for the lymphatic system in the clearance of cerebrospinal fluid from the brain and spinal cord.

Along these lines, Dr. John Paul Szalai and Marco Katic (Biostatistics) were invaluable in helping us sort out complex analysis of the data in several projects.

Dr. Dimitrios Oreopoulos introduced us to the issues of kidney failure and participated in a project that assessed the impact of lymphatic peritoneal drainage on the success or failure of peritoneal dialysis.

Dr. Bernie Boulanger and I engaged in an analysis of lymphatic drainage of the pericardial space.

Dr. Yeni Yucel and Dr. Neeru Gupta and I studied lymphatic drainage of the eye.

Finally, one of my most important collaborators was Dr. John Semple. John and I have been friends for many years and we have worked together to understand the factors that contribute to post-surgical lymphedema. Our projects have benefited enormously from this collaboration and I have learned much about the clinical complexities of this condition from John.

You have always had a productive and friendly lab staff. Can you highlight some of your key personalities in your staff over the years?

In terms of technicians, I have been privileged over the years to have some very talented people work with me. Mel Walker was my first technician and our early work provided the foundation for my career. Helen Rodela was a key individual in our studies of the role of lymphatics in peritoneal dialysis. Dianna Armstrong was the life and soul of our lab for many years and provided leadership and guidance for a large number of students and fellows. When confronted with the myriad problems in running a lab, my favorite refrain was, Dianna please take care of it! Sara Moore took over from Dianna after her retirement and did a wonderful job of keeping the lab afloat until my retirement. I am indebted to all of these amazing people.

Can you list some of your key Research Fellows (MSc and PhD)? What characteristics or components of their personalities played a part in how successful they were in your eyes?

I have been fortunate to have many remarkable students and fellows over the years. It is very difficult to select out a few for special mention as each and every one of them has made important contributions to our research. However, I feel that I should mention my very first PhD student as he had a significant impact on the development of my career. Dr. Radu Elias arrived in my lab as I was attempting to get my career started at the University of Toronto. Radu has an incredible intellectual curiosity and great talent at designing devices for experimental analysis. His work provided the foundation for my early career and I am deeply indebted to him. I thank Radu and all of the other students who have enriched my life and career immeasurably.

What are the key discoveries in lymphatic research over your career that you think are important contributions to a better understanding of lymphatics.

The most important advances in lymphatic research have come from molecular biological studies. We now know the agents that control the differentiation of venous endothelial cells into a lymphatic phenotype and how the new vessels grow and eventually separate from the veins to form the blind ending lymphatics. There is also exciting new data outlining the role of this system in cancer progression. These data may contain clues as to the development of strategies to inhibit the metastatic spread of cancer. Many excellent reviews are

available which outline the impressive progress made in this area over the last decade or so.

In addition to the aforementioned, significant progress has been made in understanding the physiology of the system. For example, it is now generally understood that the contractile properties of the vessels have a major role in lymph propulsion and that this activity can be modulated with a variety of chemical agents. We also have a better understanding of the role of this system in the drainage of extracellular fluid from tissues and organs (cerebrospinal fluid removal from the brain for instance). Along these lines, several elegant studies demonstrated that interstitial fluid pressures become more negative in inflammation, a finding that has important implications for lymphatic function.

Where do you think lymphatic research is going in the next 5 years?

While I am generally optimistic about the future, there is room for improvement in the area of education. Lymphatics receive very little attention in University courses or indeed, in Medical School. Until this changes, we will not see the critical mass of investigators necessary for real progress in the development of new treatments for lymphatic disease. Nonetheless, there has been significant progress in the basic biology of the lymphatic system. The one area that has outperformed all others in this field, relates to our understanding of the molecular regulators of lymphatic development and lymphangiogenesis. We all hope that this molecular foundation will provide new targets for therapeutic intervention in the various forms of lymphedema. However, if our experience in other areas of research is anything to go by, the application of this information to patient treatment will be difficult and slow. Stem cell therapies are all the rage in some disciplines but their application to lymphedema is difficult to predict at least in the short term. Primary lymphedema is especially problematic.

However, I believe that the best results for secondary lymphedema will be in the area of prevention rather than treatment. Indeed, there is promising evidence that lymphatic filariasis may be completely eradicated by preventing the spread of the microfilaria to mosquito hosts with drugs.

Along these lines, I suspect that it will be more beneficial to prevent the secondary lymphedema associated with cancer therapy than attempting to treat it after the edema has become entrenched. By identifying those individuals at greatest risk (genetics, physiological issues, pre-clinical edema studies, molecular markers etc.) and treating them conservatively, we may be able to reduce the incidence of lymphedema significantly.

In terms of basic science, I am certain that our molecular understanding of this system will continue to grow. However, our knowledge of the physiology of the system will progress more slowly unless we train a new generation of 'classical' physiologists (a group that can see extinction on the horizon). Lymphatic physiology is not a 'sexy' area of research and yet, there are many important issues that need to be addressed. From my perspective as a pathophysiologicalist, I would have been keen to address the following questions if I were now starting my career.

- What are the mechanisms by which radiation depresses lymphatic function? Can we prevent radiation-induced lymphatic injury with drugs?
- Why is the removal of the lymph node (as opposed to the injury of the lymphatic vessels) so important for lymphedema development? How does the lymph node excision affect interstitial fluid pressures in the drainage area of that node?
- Can one predict the development of lymphedema by monitoring interstitial fluid pressures pre- and

post-surgery?

- Can pharmaceutical modulation of the contractile properties of the lymphatic vessels be used to enhance lymph flow if appropriate in certain diseases? For example, can one increase cerebrospinal fluid drainage by instilling lympho-active drugs into the nasal cavity?
- Do we need to consider the role of the lymphatic system in the physiological adaptations that occur in microgravity conditions (space travel)?

With the closing of the “Johnston lab” so ended an era of one of the most productive and well funded basic science research labs dedicated to investigating the lymphatic circulation. Productivity came in the form of intense study, a steady stream of enthusiastic graduate students, Post Doctoral Fellows and strong collaborations with other investigators. During his career Miles had other many other pursuits outside the lab including fast cars, good wine and sailing. Miles now lives with his wife Carol in the countryside outside of Toronto and is enjoying his free time to pursue his many other interests