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**INVITED LECTURE PRESENTED AT
THE CANADIAN SOCIETY OF PHARMACOLOGY
AND THERAPEUTICS ANNUAL MEETING**

**DRUGS AND PEOPLE I HAVE KNOWN:
45 YEARS IN CLINICAL PHARMACOLOGY**

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Montreal May 27, 2011

ABSTRACT

At the Canadian Society of Pharmacology and Therapeutics Annual Meeting in Montreal on May 27, 2011 Richard Ian Ogilvie, Professor Emeritus of Medicine and Pharmacology at the University of Toronto was invited to present a lecture regarding his 45 year career in clinical pharmacology in Canada. In the lecture he identified the people and events that shaped his accomplished career.

INTRODUCTION

This lecture provides an opportunity to review interactions with my teachers, mentors, fellows and associates over 45 years in Clinical Pharmacology. My teachers and mentors include several who have resonated strongly in pharmacology such as Lucas, Kalow, Best, Ruedy, Melville, Nickerson and Beaulnes. I rarely think of any drug, trial, investigation or concept, without associating a person with it: thalidomide (Kalow, Kelsey), mersalyl (Melville), acetazolamide (Zborowska, Klassen), ethacrynic acid/furosemide (Ruedy, Perez), chlorthalidone (Tweeddale), digoxin (Ruedy, Klassen), theophylline (Mitenko, Piafsky), tolbutamide (Zinman, Loubatières), α -methyldopa (Oates), timolol (Dorian, Achong), diazoxide (Sitar, Nadeau), amantadine (Aoki, Sitar), adverse drug reactions (Ruedy), non-medical use of drugs (Beaulnes), teaching pharmacology (Ruedy), prescribing models (Kreeft), plateau concentrations (Mitenko), hypotension, drug withdrawal (Rangno), forearm circulation/metabolism (Klassen), and models of the circulation (Larochelle). Many organizations that promoted clinical pharmacology in Canada have names embedded in my memory: CFAT (Murphy, Nash), ASPET, IUPHAR (Melville, Sjoqvist), Oenophile Society (Ruedy, MacLeod), and CSCP (Sellers, MacLeod, Mahon). Over 50 residents and fellows have assisted me in research and teaching. My career as an individual, rather than a population clinical pharmacologist, has been populated with many people! Interactions between people are even more interesting than interactions between drugs. It is my fondest hope for many more, *Tout Jour à Fin!*



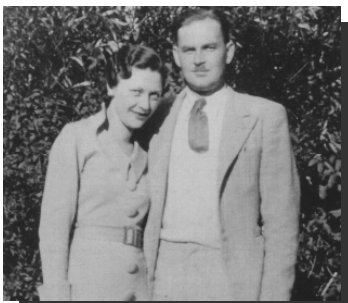
Success of Dundee Master Patrick Ogilvie 1755-80.

Ancestry

I often speculate that my career in Clinical Pharmacology was predicated by a clinical trial from 1747. My ancestor, Captain Patrick Ogilvie, who lived from 1730 – 1780 was master and owner of the ship *Success of Dundee*. Two other Scotsmen, James Lind and James Cook, were contemporaries, and in fact, he was a neighbour of Cook in East London for the last part of his life. *Success of Dundee* was a snow-rigged ship about 100 feet long with masts 95 feet above the deck. It carried 80 tons of cargo between Dundee and London and the North Sea, the Baltic, the Mediterranean, Caribbean and Atlantic Oceans and the shores of America. To survive time at sea longer than two weeks, he had to have knowledge about prevention of scurvy.

In 1747 James Lind carried out a trial at sea using two groups of 12 men with advance symptoms and signs of scurvy. He kept them in hammocks in the forehold and fed them *one diet common to all* for fourteen days, but divided one group into six pairs for supplementation with cider, elixir of vitriol, vinegar, seawater, a paste of roots and seeds, or two oranges and one lemon a day, for six days. The last two men recovered and returned to full duty before the trial ended. (*see Stephen R. Bown, Scurvy, Toronto 2003 and Madness, Betrayal and the Lash, Vancouver 2008 for additional details.*) In the age of sail, scurvy was responsible for more deaths at sea than storms, shipwreck, combat and all other diseases combined. Although prevention and cure was known from Lind's work, similar to modern times, politics and non-repetition of trials, along with failure to produce a stable source of ascorbic acid resulted in failure to implement anti-scorbutic diets in the entire Royal Navy until 1795. However, near the end of the War of American Independence when the French and Spanish sided with Americans against the British, the West Indies fleet of the Royal Navy was at full complement of sailors. Judicious use of oranges, lemons and limes for the 21,000 men, reduced scurvy and other diseases from 1 in 7 to 1 in 20 men. The British defeated a much larger fleet of French and Spanish ships at St. Lucia in 1783, preventing the loss of Jamaica from the British Empire. My father was born in Jamaica in 1905.

Dad finished high school in England and immigrated to Canada, actually to Alberta where an Uncle from Jamaica was a Psychiatrist at the Ponoka Mental Hospital. He graduated from the University of Alberta in Mining Engineering and Geology in 1930, supported by success in gambling at Bridge, which he claimed was a mathematical skill. Of course during the *Great Depression* he had no job offers until 1935 so he supported himself in part by being an orderly at the Ponoka Mental Hospital where he met my mother who was a head nurse on one of the wards. His first job in Mining was in Sudbury with INCO in 1935 where I was born.



Mom and Dad, Ponoka Alberta 1935

Dad was the first to educate me that drugs have more than one effect, beneficial or adverse. In 1946 he developed pneumonia, which was cured by the first antibiotic penicillin that had been mass-produced during WW II. This was a beneficial effect, but at the same time his skin exfoliated, the adverse effect. He was given a cough medicine that was very effective in reducing the cough, the beneficial effect, but additionally he raved about better “*high*” than any other drug he'd ever used! The cough medicine was of course heroin.

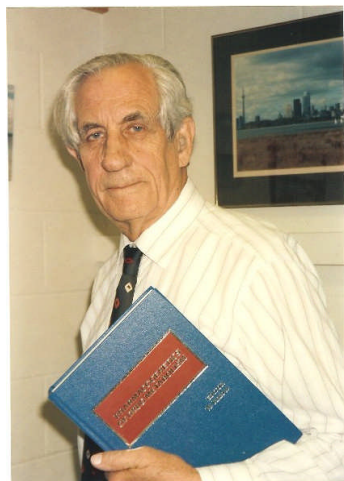
Education



George H Lucas

During high school, I developed an interest in both medicine and dentistry but chose dentistry, believing that I would retire by the age of 55. Here I am almost 75 still working in medicine!

I did two years of dentistry, but hated it. I asked a friend, Bill Lucas, who was studying medicine, to introduce me to his father, George Lucas, for advice on how to transfer from dentistry to medicine. Dr. Lucas was a brilliant chemist who worked for Fred Banting in the mid 1920's. Banting persuaded Velyien Henderson, who was then the Chair of Pharmacology at University of Toronto, to hire him. In 1928, Lucas isolated cyclopropane, a very effective anaesthetic agent, but unfortunately, with explosive properties. In that time, pharmacologists always used themselves as guinea pigs. Lucas, Henderson and Banting were among the first volunteers for cyclopropane anesthesia. Dr. Lucas introduced me to the concept of clinical drug assays, as he had a laboratory for *doping*, but it wasn't *doping* of athletes, but for race-horses.



Werner Katlow

Now in medicine, I was exposed to two widely celebrated investigators, the physiologist Charles Best, who with Banting brought insulin into clinical use, and Werner Kalow, at that time a recent immigrant from Germany, who taught us Pharmacology.

Werner went on to a brilliant career, developing the field of pharmacogenetics. I was somewhat frustrated with his lectures since I had difficulty understanding his heavily accented English, and found the Pharmacology textbook by Gaddum to be less than helpful, having been written in the 1930's, followed by sporadic updates. Certainly adverse effects of drugs were not mentioned. When I started practice as a GP in my hometown of Copper Cliff in 1961-62, I actually prescribed thalidomide, which had been approved in Canada in April 1961, withheld and then withdrawn in the USA due to the efforts of Frances Oldham Kelsey in 1962.

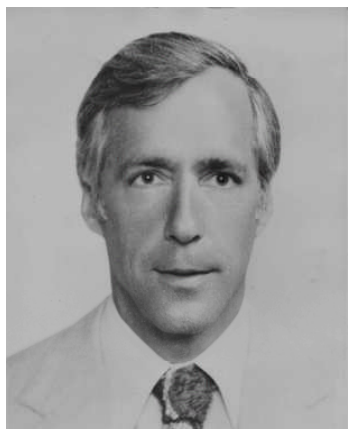


***Frances Oldham Kelsey BSc MSc
(McGill) PhD MD (Chicago)***

Kelsey was given a special honour by President Kennedy for her perseverance in preventing the release of thalidomide. Many of you will not realize she is a Canadian, born on Vancouver Island, who did her Bachelor of Science and Master of Science in Pharmacology at McGill before going onto Chicago for a PhD and MD. Largely as a result of her efforts, the Food Drug and Cosmetic Act of the United States, was modified in 1962, requiring data on efficacy as well as safety from controlled studies. As a result, the FDA was restructured, and Phases 1 – 4 of clinical studies were defined. This was a major stimulus for training of Clinical Pharmacologists.

Of course thalidomide is no different than other drugs, having both beneficial and adverse effects. Currently it is used in the treatment of leprosy and multiple myeloma.

Training in Clinical Pharmacology



John Ruedy, MD

Two other drugs prompted me to consider clinical pharmacology as a career. When I entered medical practice, the only parenteral diuretics were mercury such as mersalyl acid, often potentiated by concurrent administration of theophylline. I was certain that several of my patients succumbed during administration of these agents and was curious as to the reason.

My senior resident during the medical rotation as an intern at the Toronto General Hospital was John Ruedy. He subsequently became my mentor in clinical pharmacology. After a year of general practice, I began training in internal medicine at the Montreal General Hospital where Ruedy was chief resident.

Ruedy went to Manitoba to begin a career in Clinical Pharmacology in the Department of Pharmacology headed by Mark Nickerson. While still in Manitoba, he persuaded me to undertake a prospective study of adverse drug reactions during hospitalization during my final year in Internal Medicine at the Montreal General Hospital.¹

This was the second article in the world on this topic and showed an 18% incidence, attributing to 25% of in-hospital deaths while doubling hospital stay. Surprisingly, 60% were due to drugs in several years such as digitalis, quinidine, anti-microbial agents, insulin and diuretics prompting us to consider educational techniques to alter the problem.

Ruedy returned to McGill and we set up a prospective survey of consequences of digitalis therapy over a one-year period and found that 22.9% received digitalis therapy in hospital and 21.4% of digitalis courses resulted in intoxication. We then embarked upon an educational program to guide residents in digitalis therapy. The subsequent year, the intoxication rate was halved to 12.4%.² We altered physician habits by providing easy-to-use instructions directly related to actual indications for the drug in clinical practice.

In 1980, John Kreeft and I began to develop a computerized system of prescribing based on these principles of clinical pharmacology, but failed to find funding from the NIH or other agencies. I am certain that applying principles such as identifying goals of therapy, understanding kinetics in individual patients, defining and monitoring for efficacy and toxicity, combined with prompts and flags to the physician and pharmacist, would greatly improve therapeutic interventions, truly patient-specific.

Thirty years later we still do not have an adequate system.



Kenneth Melville MD

I became John Ruedy's first resident in Clinical Pharmacology in 1966. He introduced me to the Chair of Pharmacology at McGill at that time, Ken Melville. Some of you may not realize that McGill has taught Pharmacology since 1824 and has the oldest department in Canada. Melville was born in Jamaica, a contemporary of my father. He had an early interest in mercury diuresis which we will return to later. He became the 10th Chair of the Department in 1952 (all had a MD!).

In 1960 he was arrested with 7 other Black physicians attending a medical congress in Atlantic City when the cafeteria refused to serve them. He organized a meeting during the International Congress of Physiology in Montreal in 1953 that led to the establishment of IUPHAR, separate from IUPS. Within a day of meeting him, he had organized travel support to the 1966 ASPET meeting in Mexico City.



Mark Nickerson PhD MD



Aurèle Beaulnes, MD
Aurèle Beaulnes MD

Ruedy enticed Mark Nickerson to succeed Melville as Chair of Pharmacology. Many of you will know that Nick was forced out of America by Senator McCarthy's Committee on Un-American Activities when he pleaded the Fifth Amendment and lost a tenured job at Ann Arbor, Michigan. It is chilling to hear a recording of Nick's testimony on the Web.

I find it quite ironic that phenoxybenzamine, introduced into clinical use by Nickerson, is the only drug I regularly have to ask Health Canada for permission to use! Nick had an acid-tongue. When Furchgott promoted his idea of endothelial-relaxing-factor using blood vessels of turkeys, Nick commented that Furchgott did not know the difference between a turkey and a vulture. Not surprisingly, Nick's first post-graduate degree was in avian embryology. He appointed another supporter, Dr Aurèle Beaulnes to the department after Beaulnes finished his term as the founding Director of Department of Pharmacology at Université de Montreal.

Dr Beaulnes spent countless days lobbying government and industry, writing papers and giving talks throughout the country. Beaulnes gave me sage advice about the politics of Clinical Pharmacology.

Returning to diuretics, a 1928 paper in JPET by Melville and Stehle³, who at that time was Chair of Pharmacology at McGill, concluded that diuresis with mercury diuretics was in part due to an extra-renal action. The loop-diuretic, ethacrynic acid came into clinical use when I started in Clinical Pharmacology with Ruedy in 1966. Using it to promote diuresis in patients with acute heart failure, I noted cardiac function often improved before diuresis had occurred and wondered about extra-renal actions of ethacrynic acid. This prompted a series of studies in animals and man demonstrating a direct vascular action of ethacrynic acid, with an unknown mechanism. Ethacrynic acid caused hearing loss so was replaced by furosemide, which also had vasodilator properties.

At the same time, I was working with Gerry Klassen, a Cardiologist at the Royal Victoria Hospital. Danuta Zborowska, a research fellow in Klassen's lab, was interested in lactic acidosis induced by hyperventilation and cardiovascular shock. I suggested we try acetazolamide to block lactate production, since largest tissue content of carbonic anhydrase, is the red cell mass. We showed acetazolamide could prevent hyperlactatemia of hyperventilation and postulated that prevention of high-altitude mountain sickness by acetazolamide was due to this action.⁴ This mechanism was never accepted.

The critics were right but it wasn't until 39 years later in 2009 that it was shown that high altitude climbers actually did not produce lactic acid in spite of being hypoxemic and hyperventilating.⁵ Meanwhile at the Montreal General, we established a hypertension clinic and initiated a series of dose-response clinical trials with the diuretics hydrochlorothiazide, spironolactone and chlorthalidone.⁶⁻¹¹ Ruedy was adamant that a prime thing that differentiated Clinical Pharmacologists from other physicians was knowledge of dose-response of beneficial and adverse effects of drugs.

Hypertension, Diabetes and Cardiovascular Clinical Pharmacology

One of our most widely quoted clinical trials in hypertension was the chlorthalidone dose- response using a Latin-square design of doses 25 to 200 mg a day each over eight weeks with placebo intervals. We demonstrated that 25 mg a day was the most efficacious and safest dose to lower blood pressure while preventing adverse effects on potassium, urate and kidney function.⁹ I tried to persuade the manufacturer distribute a 25 mg dose of chlorthalidone, but was unsuccessful. Even to this day when chlorthalidone is being rejuvenated as an anti-hypertensive drug, we only have 50 and 100 mg tablets in Canada. Because of its long half-life, doses above 25 mg a day can be problematic.

Interestingly, chlorthalidone has been found to be active against several carbonic anhydrase isoenzymes allowing increased production of nitric oxide, perhaps a mechanism underlying vasodilator action of diuretics. Indapamide is also active in this system, but not hydrochlorothiazide.¹²

Spironolactone is another drug increasingly used in the clinic. Forty years ago we undertook a dose-response trial up to 400 mg a day. Increasing doses induced a progressive reduction in systolic, but not diastolic blood pressure.¹⁰ Perhaps this is in part due to changes in function (and later structure) of large conduit blood vessels and the heart underlying the current use of spironolactone in resistant hypertension and congestive heart failure.

The next drug we turned to was tolbutamide, used to treat diabetes. The UGDP Study suggested increased cardiovascular deaths with tolbutamide vs. placebo.¹³ The recent story of rosiglitazone, Avandia, is perhaps comparable.^{14,15} Could tolbutamide have an effect on peripheral tissues in man including the heart? We used an isolated perfused forearm experiment, where we created local drug concentrations to study effects on skeletal muscle, separate from fat and skin, without problems created by systemic drug effects. We were the first to study the metabolic effect and uptake of digoxin in man.^{16,17} Bernie Zinman, while training with us in Clinical Pharmacology, undertook to study the effects of tolbutamide. This was the first demonstration that tolbutamide had no effect on glucose uptake of muscle, fat or skin in man.¹⁸

In 1975 during a sabbatical year at Montpellier, France, I had the opportunity to review these findings with the pharmacologist who first initiated the use of sulfonylureas in diabetes, Prof. Auguste Loubatières. During the early part of the WWII, his colleague, Dr. Jamboff had noted some experimental sulfonylureas, used for antibacterial activity, reduced blood sugar. Loubatières did studies in animals showing an effect on the pancreas and liver and came up with an effective molecule that was subsequently modified as the initial sulfonylurea used in diabetes. On relating our forearm experiments on putative peripheral effects of tolbutamide, he gave an enigmatic smile while saying “*pas possible!*” We then turned to forearm studies on the vascular effects of anti-hypertensive drugs in man using plethysmographic strain gages, including diuretics, beta-blockers and calcium channel blockers.¹⁹⁻²³



Mont St. Hilaire 1976

Advancing Pharmacokinetics



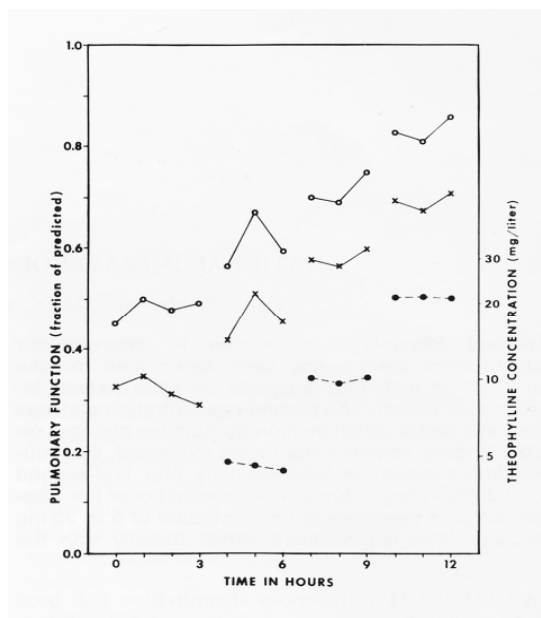
Paul Mitenko MD

Our training program in Clinical Pharmacology now included two-years of course work in kinetics, drug transformation, disposition and toxicity, statistics and clinical trial design and analysis.

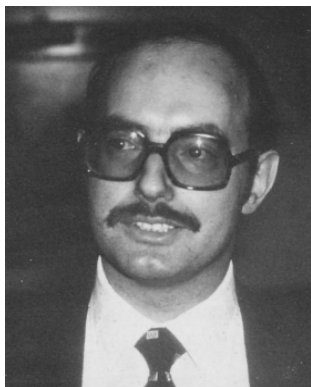
Forty-seven residents and fellows participated from 1967 – 1983. One was Paul Mitenko, who fortunately for me, had a degree in Math and Physics. His wife Donna was similarly trained. We asked Donna to give our residents (and me) a crash course in Calculus so that we could teach kinetics.

I asked Paul to consider ways to rapidly achieve steady-state drug concentrations in man so we could study dose-response relationships. He had the brilliant and simple approach of using the maintenance infusion rate as *beta times the initial bolus* where beta was the slow disposition constant.²⁴ I wanted to return to the problem of theophylline so we applied this to theophylline kinetics and studied a series of patients with asthma in a 12-hour experiment with 3 hours each of placebo followed by three loading and maintenance doses of theophylline to establish plateau plasma concentrations of 5, 10 and 20 µg per ml, while we repeatedly measured respiratory function.²⁵

We were able to develop dose recommendations for use of parental theophylline. The resultant publication in 1973 was highly cited over the next five years. It led to the development of a sustained-release tablet of theophylline, Theodur, and of course application in *therapeutic drug monitoring*.



Plateau plasma theophylline concentrations and respiratory function



Ken Piafsky MD

Another resident, Ken Piafsky, carried out multiple studies dissecting the interaction of disease and drugs with theophylline. After his training with us, he went off to Karolinska Institute to work with Folke Sjoqvist. As you realize, our Society has an award named after Piafsky. Tragically he died from leukemia shortly after returning to Canada and joining Ed Sellers and Stuart McLeod at the Toronto Western Hospital.

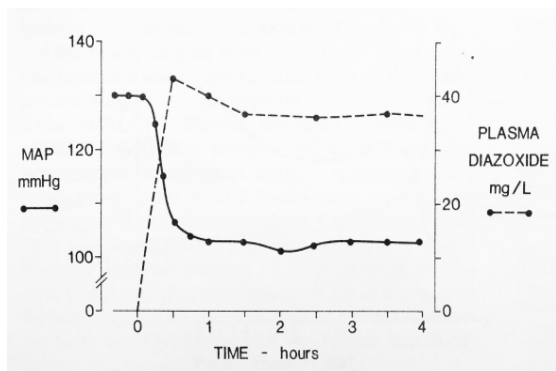
Of course theophylline, as with many of the drugs I have studied, is no longer used for its initial indication, asthma. It is used to reverse angina caused by dipyridamole during cardiac stress tests without exercise. We later studied enprofylline, which lacked adenosine receptor activity; but, this molecule caused hepatitis.²⁶ Recently, rolofylline, a selective adenosine A₁ receptor antagonist with diuretic properties, failed in a heart failure study published by Barry Massey.²⁷



Dan Sitar PhD

Dan Sitar, a Pharmacist and Pharmacologist trained in drug biotransformation and assay techniques, joined our group. With his expertise, we began other pharmacokinetic studies including diazoxide which had just been introduced as the parenteral drug most commonly used for hypertensive emergencies. The package-insert (and Ed Sellers) called for an extremely rapid bolus which resulted in a rapid, but totally unpredictable, reduction in BP. We postulated that achieving a steady state plateau, as we did with theophylline, would prove a more suitable and safe regimen.

Using Paul Mitenko's approach, we gave a more deliberate bolus followed by a maintenance dose designed to achieve a constant plateau drug concentration which reduced blood pressure and maintained it at target level, without hypotensive adverse effects.²⁸



Calculated loading and maintenance diazoxide doses and blood pressure response

Of course diazoxide is no longer used in hypertensive emergencies, having been largely replaced by parenteral labetalol or nitroprusside.



Robert Rangno MD

Around this time, Bob Rangno returned from Vanderbilt University. He had trained with us in clinical pharmacology and then worked with the group under John Oates. Oates, while working with Albert Sjoerdsma at the National Heart Institute, had carried out Phase I and Phase II-type trials of α -methyldopa in man after Merck had finished 3-month animal toxicity studies in late 1959. Merck insisted the drug had no effect on BP of animals; but, Sjoerdsma and others were convinced that a dose-response study in man using gram-doses would be effective.

Can you imagine today persuading an Ethics Committee to allow administration of α -methyldopa to man? Seven months later, Oates had a paper in *Science* showing it had hypotensive action after oral administration and with no more than 50 trial subjects, it became part of our anti-hypertensive armamentarium in 1962 and within 10 years was one of the top-selling drugs in the world. Currently, Phase I and Phase II trial subjects number in the 1000's. Methyldopa of course has withstood the test of time in hypertension during pregnancy and for resistant hypertension.

Rangno and David Shand had undertaken a number of beta-blocker withdrawal trials and developed recommendations for safe withdrawal. He set up the intensive care unit at Montreal General Hospital so our clinical pharmacology group now ran almost the entire hospital, having a General Medical Ward, Intensive Care Unit, Clinical Toxicology, Infectious Disease, Clinical Pharmacology, Pharmacy Committee and Clinical Trials Ethics Committee, under its wing. I learned all I know about autonomic nervous system dysfunction from Bob. Of course he is the founding president and only member of the Canadian Hypotension Society that was started at the same time as the Canadian Hypertension Society. Its motto, *Pressio sanguinis tensa est mellior quam nulla pressio*, translates *some blood pressure is better than no blood pressure at all*.

Timolol is a drug of interest, being the only beta-blocker discovered in Canada (by Frosst). A trial in Norway introduced the concept of beta-blocker induced reduction and mortality and re-infarction in 1981²⁹ and in fact, timolol caused the greatest reduction of all beta-blockers subsequently studied, yet disappeared from use for some reason I cannot fathom. We did the initial studies on intravenous timolol with Mike Achong and Ken Piafsky.^{30,31} Today, timolol is used almost exclusively for the treatment of glaucoma.

We undertook a number of clinical trials of beta-blockers in hypertension³²⁻³⁵ and at the same time I developed an interest in the effect of physiology and drugs on conduit vessel function including the concept of augmented systolic blood pressure due to lack of compliance of conduit vessels and reflected pressure waves causing augmented systolic pressure and adverse effects. In older patients we now recognize beta-blockers augment SBP and fail to provide benefit in hypertension in the absence of coronary disease or dysrhythmia.



Pierre Larochelle MD PhD

All along I had a great interest in integrative function of the cardiovascular system and applied many mathematical models to the circulatory system using experiments in dogs and pigs. This was certainly aided by Pierre Larochelle, who, as a PhD candidate in Pharmacology at McGill, chose me as his thesis advisor. I found this quite strange having no formal training in basic science. With Pierre in the lab I was able to formulate many of the concepts that I carried through the next 25 years in experimental pharmacology, involving studies on total vascular compliance and capacitance in hypertension and heart failure, and the effect of drugs used in those conditions.³⁶⁻³⁸ In fact, ¼ of my peer-reviewed publications were with MRC funding of these concepts. I was proud to have 27 years of continuous support from MRC.

Although there was not much impact from these studies in the academic world, I found the concepts useful in writing a chapter in the last edition of the University of Toronto pharmacology text on vasodilators and the treatment of hypertension.³⁹ It allowed me to integrate pathophysiology and pharmacology into clinical medicine.

Clinical Pharmacology in Canada

Now it is time to insert a few comments on how Clinical Pharmacology was developed and progressed in Canada. In large part, research-based PMAC is responsible for its initial funding support, having established the Canadian Foundation of Advancement of Therapeutics (CFAT) in 1963 with funds from individual pharmaceutical firms.

Physicians instrumental in the early part included C. Walter Murphy from Ciba-Geigy and Peter Nash from Abbott. Other active supporters included Will Dorian from Merck, Dick Davies and later Don Zarowny from Ayerst McKenna, and Ray Fines from Astra. CFAT supported individuals and then entire groups in Clinical Pharmacology across Canada. Millions of dollars were spent in the first few years.



Peter Nash MD



Will Dorian MD

As a result of individual contacts, our group was given several drugs to undertake Phase I and Phase II studies including an anti-epileptic, isosorbide mononitrate, amoxicillin and timolol, the last provided by Will Dorian at Merck Frosst. He later volunteered as Executive Director of our Society for several years.

I hired Will's son Paul, back from the States. He had trained in Clinical Pharmacology with Ed Sellers, then Cardiology at University of Toronto and then electrophysiology in the States. Paul has gone on to a stellar career in clinical pharmacology of anti-arrhythmic therapy.



Canadian Foundation for the Advancement of Therapeutics 1979

We spent a sabbatical year in the South of France at Montpellier and returned to Mont St. Hilaire and found myself increasingly in administrative positions.

I was a member of the CFAT along with other clinical pharmacologists including Bill Mahon, Tom Wilson, Albert Nantel, John Ruedy and other members from the PMAC.

We morphed annual meetings of our *Opimian Society* at CSCI meetings started by John Ruedy, into the Canadian Society for Clinical Pharmacology. Stuart McLeod was instrumental as the ongoing scribe. Stuart and Ed Sellers worked on the incorporation of the Society in 1979 and the inaugural meeting held in 1980 had me as President, Stuart as Secretary, and Bill Mahon, Fred Aoki and George Carruthers as members of Council. I was a founding director of the Canadian Hypertension Society in 1978 and subsequently President 1992-3, and was Editor of *Hypertension Canada* from 1989-2008.

Steps Along the Way

At the MGH Division of Clinical Pharmacology I was the director from 1976 – 1983. We had a staff of 8 physicians and 1 PhD. In 1978, I succeeded John Ruedy as the 13th Chair of Pharmacology and Therapeutics at McGill. From 1977 – 1987, I was a member of the Clinical Pharmacology section of IUPHAR and chair for three years. I moved to the Toronto Western as Director of the Divisions of Cardiology and Clinical Pharmacology in 1983. As you may know, I became Professor Emeritus in 2002 and continue to work in the Hypertension Unit.

There have also been many drugs that I have worked on over the years. Perusing the list of drugs that I helped develop the dose recommendations for clinical use, you can deduct that only a few remain in constant clinical use, which I suppose is good, as it means there must be new compounds providing more work for other clinical pharmacologists.

Theophylline	Procainamide	Amoxicillin	Midazolam
Diazoxide	Lidocaine	Gentamicin	Isoxicam
Furosemide	Disopyramide	Metronidazole	Cyclosporine
	Digoxin	Ceftriaxone	
		Amantadine	

I have not been able to mention all of my colleagues, students, residents and fellows who have taught me, mentored my activities and made it possible for me to function as a physician and Clinical Pharmacologist. Once again I thank the Canadian Society of Pharmacology and Therapeutics for giving me this opportunity to walk down memory lane.

In summary, my life as a Clinical Pharmacologist has been largely dedicated to individual rather than population clinical pharmacology; an attempt to meld pathophysiology of symptoms and disease to pharmacological treatment, with a special interest in dose-response relationships for beneficial and adverse effects, using applied pharmacokinetics, systematic observation and measurement, followed by clinical trials and reverting to animal studies when I could not do the investigation in man. My career as an individual rather than a population clinical pharmacologist has been populated with many people! Interactions between people can be far more interesting than interactions between drugs.⁴⁰⁻⁴⁷ It is my fondest hope for many more, *Tout Jour à Fin!* (mottos of my family).

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