Discovering Canada’s Oral Tradition: Dental Research in the Second Half of the 20th Century*

Richard P. Ellen

Part 2: Strengths, Innovations, and New Directions in Dental Research in Canada

Canadians are avid sports fans, and Canada has excelled in sports by being selective: ice hockey, figure skating, speed skating, freestyle skiing, synchronized swimming, rowing, and even professional baseball when it is fully funded. Similarly, due to the relatively small size of the dental investigator pool and perhaps to an insufficient per capita investment in biomedical research, Canada’s internationally competitive dental research has concentrated in a few principal disciplines. In 1986, MRC conducted a comprehensive review of dental research in Canada under the chairmanship of J.B. Macdonald (Macdonald et al., 1986). The report recognized the preeminence of Canadian dental research in the following six areas:

Biomaterials

Canadian investigators have been international leaders in dental and bio-materialism for a few decades. For example, research in the early 1960’s by W.V. Youdelis, D.K.K. Innes, and G.H. Sperber at Alberta was crucial to the development of the new generation of copper-silver dispersion-strengthened amalgams found in today’s products. Recruitment of Dennis Smith to Toronto in the late 1960’s began a new era in materials science research in Canada. Already a co-originator with J. Charnley of acrylic cements for artificial joint fixation and the inventor of the polycarboxylate cements that revolutionized restorative dentistry, Smith contributed to the characterization and assessment of glass-ionomer cements and dental resin composites in the 1970’s and 1980’s. He then pursued trace element analysis and biocompatibility as part of Toronto’s MRC Program to develop new implant materials and designs. In 1987, the Government of Ontario established a provincial center of excellence, the Ontario Centre for Materials Research, that links research at several universities. Smith was the first Director of the Biomaterials Research Centre in Toronto, succeeded by Robert Pilliar in 1994. Dennis Smith has been awarded innumerable international and national awards and honorary degrees. He even made the national news when his ailing hips became recipients of his own innovation in implant cements and porous-surfaced orthopedic implants, a Pilliar invention. There is also competition at the federal level for national networks of excellence, and a proposal to establish a biomaterials network directed by John Davies and titled “Engineered Materials; Biomolecular Materials and Devices” was one of three finalists for consideration in June, 1995.

The biomaterials research laboratory at Dalhousie also has a fine international reputation for its synthesis of glass, ceramic, and polymer biomaterials. It is funded by both University-Industry and MRC-Industry awards. Derek Jones, the lab’s leader and recent CADR President, has received the Wilmer Souder IADR Distinguished Scientist Award for his contributions. He served from 1990-94 on the Advisory Panel on Advanced Industrial Materials to the Federal Cabinet. Jones was also included in the national biomaterials network proposal.

Connective tissue biology

Canada has had a long line of investigators who have studied the lineage of stromal cells in oral connective tissues, their functions in tooth development, matrix turnover, and wound healing. Tony Melcher, C.A.G. McCulloch, and co-workers have led the dental community in tracing the progenitor cells in healing periodontal wounds. The periodontal treatment modality “guided tissue regeneration” is basically a clinical interpretation of their fundamental science. Jane Aubin and Jaro Šodek’s labs have determined cell markers associated with differentiation in bone cell lineages and, with Johan Heersche, have initiated studies on intercellular communication via cytokines and hormones regulating differentiation. Heersche, his former student H.C. Tenenbaum, and more recently J. Davies have developed novel in vitro systems by which regulation of osteogenesis can be investigated. Using these systems, Tenenbaum and I have opened up a new direction, studying inhibitory effects of periodontal pathogens on bone formation. Jack Ferrier’s and Jane Aubin’s former student Jeffrey Dixon (Western Ontario) is doing significant work on the cellular physiology of osteoclasts.

Matrix renewal is a fundamental feature of connective tissue homeostasis. As early as the mid-1960’s, Canadian researchers were postulating new mechanisms of collagen turnover. Anders Bennick and Murray Hunt published one of the first accounts of collagenase activity in the gingiva. Then, in the early 1970’s, A.R.

*Unabridged manuscript available from author on request
Ten Cate and D. Deporter introduced the concept that collagen remodeling in native connective tissues and healing wounds was accomplished primarily via phagocytosis of collagen by fibroblasts, work that is still continuing in McCulloch's lab. Jaro Sodek broke into the dental field in the 1970's with his timely investigations of collagen turnover in periodontal tissues, and in the 1990's, his work on regulation of bone sialoprotein and bone morphogenetic proteins is still at the leading edge. Significant research on collagenses and other matrix metalloproteinases has come from his lab and from the labs of Paul Scott (Alberta) and C. Overall (UBC).

**Epidemiology**

Canada has yielded a high prevalence of leaders who have helped establish the methodology for survey and health services research. By the late 1950's, Robert M. Grainger had established himself as a national leader. He was the key person in biometrics at Toronto; among other innovations, he designed the analytical strategies for the Burlington Growth Study. Under his leadership, the Faculty of Dentistry installed a new invention called a computer long before the other faculties on campus. In 1959, in cooperation with the CDA, he published a manual for the evaluation of Canadian dental health that established Canada as one of the first countries to set national standards for epidemiological surveys. Grainger went on to become a key figure among those who put together the WHO dental survey criteria. In the 1950's, Ontario was also a center of attention due to the well-designed water fluoridation study in Brantford, under the leadership of Harry K. Brown. The study was the first to include both naturally fluoridated and non-fluoridated control cities. In the 1960's, Robert Rомнке contributed a landmark study on the utility of dental auxiliary personnel in Canada's tiny province, Prince Edward Island. John Stamm (McGill) contributed a series of important studies on dental caries and fluoride use in Quebec. In the 1970's, George Beagrie was an important team member who helped WHO develop its periodontal and other dental needs survey strategies, and Murray Hunt led the group that conducted the WHO international collaborative study of oral health in Canada. In Quebec, Jean-Marc Brodeur, current Head of Epidemiology at the Faculty of Medicine, Montreal, contributed key investigations of manpower demands and services and surveys on fluorosis. There are several groups and individuals who have conducted and continue today to contribute significant epidemiology and large-cohort studies in oral aspects of gerontology and delivery of dental services to the elderly: David Banting (Western Ontario); James Leake, David Locker, and Donald Lewis (Toronto); Amid Ismail (Dalhousie); Daniel Kandelman (Montreal); Michael MacIntee (UBC); and Gordon Thompson (Alberta).

**Growth and developmental biology**

Canada's reputation for research in craniofacial development has experienced a growth spurt since the early 1950's, when the longitudinal studies of the Burlington Growth Centre in Toronto were conceived by Dr. Robert E. Moyers. With its original objective to test the value of interceptive orthodontics, this internationally unique study compiled growth records of a complete generation of children in the town of Burlington, Ontario, and provided research-minded orthodontists with an unparalleled opportunity to establish growth prediction templates for youngsters aged 4 to 20. For its Director, Frank Popovich, it was a life's scholarly work. His dedicated planning, conduct, and analysis, combined with Grainger's foresight in biometrics, led to 20 years of subsequent utility by Toronto's chairmen of orthodontics, E. Harvold and D. Woodside, their staff and students, as well as by investigators from around the world.

Canadians have had a strong impact on knowledge and treatment of craniofacial anomalies. In the 1960's, Malcolm C. Johnston contributed significant studies on differentiation of oro-facial tissues, before moving on to North Carolina. Brian Hall (Dalhousie) has for many years investigated the embryological development of the facial skeleton and recently its molecular regulation. Virginia Diedwet (UBC) has led laboratory studies on craniofacial morphology, with special emphasis on development of the embryonic midface and primary palate formation. She has recently been joined by Joy Richman. Together, their work has important implications in the area of cleft palate and lip. R. Bruce Ross (University of Toronto and Hospital for Sick Children) has contributed significant longitudinal clinical studies on cleft palate and lip repair and on orthognathic surgery.

Canadians are also well-recognized for their work on the development of teeth and their supporting structures and on salivary proteins that affect post-eruptive surface mineralization. H. Warshawsky (McGill), Antonio Nanci (Montreal), F.M. Eggert (Alberta), and R. Burgess and Hardy Limeback (Toronto) have all contributed to fundamental knowledge of amelogenesis during tooth development. Richard Ten Cate (Toronto) is well-known for his research on the development of the periodontium and of the dentin-pulp complex. Anders Bennick (Toronto) is an international leader in research on the biosynthesis, post-translational modifications, and functions of salivary proline-rich proteins that form pellicles on teeth and thereby affect the enameU.S. balance of surface demineralization and remineralization.

**Microbiology**

Oral microbiology in Canada today is the downstream expression of messages promoted by J.B. Macdonald and E. Marc Madlener in Toronto in the 1950's. Indeed, I studied with Macdonald's appointee Ronald Gibbons at "The Forsyth" and subsequently filled Madlener's tenured position upon his retirement. Canada now has one of the most productive national efforts in oral microbiology. Perhaps this grew from an MRC-supported workshop, Oral Microbiology Canada, chaired by Barry McBride and me in 1978. Dalhousie (Song Lee), Laval (see following paragraph), Manitoba (L. Hamilton, G. Bowden), McGill (E.C.S. Chan), Toronto (H.J. Sandham, R.P. Ellen), and UBC (B.C. McBride, V.-J. Uitto) all have federally funded investigators studying basic bacteriology or mycology. Saskatchewan (Kunio Komiyama) and Alberta (F.M. Eggert) have also contributed via support from the Canadian Cystic Fibrosis Foundation and industry, respectively. Research on periodontal organisms has concentrated on phylogenetic and chemotaxonomic classification, adhesion, proteolytic activities, cross-feeding, antimicrobial sensitivities, and cytopathogenicity. Research on oral spirochetes is being conducted at four centers, which must be some sort of international record. Research on
cariogenic bacteria has concentrated mostly on pathways and molecular biology of sugar transport and metabolism, as well as on longitudinal clinical studies, including some of the most significant contributions in the areas of caries progression, nursing bottle caries, and root-surface caries.

Special mention should be made of the great concentration of oral microbiologists and immunologists at Laval. Beginning with an idea for cooperation between Luc Trahan at the new Faculty of Dental Medicine and Denis Mayrand at the Faculty of Science and Engineering in 1977, a multidisciplinary and multitalented team has evolved into what is known as GREB (Groupe de Recherche en Écologie Buccale). “Le Groupe” accounts for about $1 million in direct research funds, principally from MRC and Fonds de la Recherche en Santé du Québec. Other members of GREB include Christian Mouton, Noëlla Deslauriers, Marc Lavoie, Christian Vadeboncoeur, Michel Frenette, Daniel Grenier, and Luc Giasson. GREB is an example of how a small dental faculty can make a very strong international contribution by concentrating on a highly focused direction and by fostering meaningful collaboration with other scientists on campus.

Neurosciences

Canada is a cerebral cortex when it comes to neurosciences of orofacial pain and masticatory function. Its development can be traced to the mid-1960’s appointment of Peter Dellow (from Adelaide) and Arthur Storey (from Toronto and Michigan) to the faculties at Western Ontario and Toronto, respectively. Shortly thereafter, Barry Sesse (Sydney and NIDR, US) joined Storey in Toronto, Jim Lund (Adelaide) completed his PhD with Dellow and was appointed to Montreal, and Alan Hannam (Adelaide and Bristol) was appointed to UBC. These investigators provided the major thrusts in Canadian dental neurosciences in the 1970’s. They recruited and trained additional personnel—Jimmy Hu (Toronto), Alan Lowe (UBC), and Gary Duncan and Catherine Bushnell (Montreal)—contributing to expansion of neuroscience research in the 1980’s and 1990’s. Rex Holland’s work on pulp neurobiology at Alberta should also be recognized. The Toronto group has concentrated mostly on cortical and subcortical mechanisms underlying mastication, swallowing, and related functions as well as on mechanisms and control of orofacial pain. Clinical pain research in Toronto has been strengthened in the 1990’s through Howard Tenenbaum and David Mock’s work on atypical facial pain and by the recent recruitment of Thuan Dao, one of Lund’s students, to the Department of Prosthodontics. The research directions at Montreal are similar and have been strengthened through the work of Gilles Lavigne on nocturnal bruxism and by interactions with investigators in implant prosthodontics. The UBC team focuses mostly on characteristics of human masticatory and tongue movement functions and their related biomechanics. Neurosciences research in Canada is supported by MRC and, for Toronto, by the US NIDR. Several of the investigators have provided leadership roles internationally—for example, as President of IADR, Presidents of the IADR Neurosciences and Pulp Biology Groups, President of CADR, and President of the Canadian Physiological Society.

Innovations at the interface with industry

Canadians love the expression “What goes around comes around”. It is a way of saying that history repeats itself or one gets what one deserves. Which Canadian dental innovation has had the most impact on its field? Self-centered on my own field, I choose the periodontal probe. Has there been a modern clinical study in periodontics that has not measured with a probe? My generation was brought up on “The Williams Probe”, the heavy one with the millimeter markings that skipped 4 and 6 for better visibility. Charlie Williams tells me that his “honorarium”—or what patent-minded researchers now call “royalties”—for inventing the “Clevdent Williams probe” was a half-dozen free instruments. In his day, what went around didn’t necessarily come back. Now I head his department, which has contributed even further to the concept of probing via the computer-driven Toronto Automated Periodontal Probe, invented by Chris McCulloch and Peter Birek. So, history does repeat itself.

Another major focus in periodontology is the analysis of crevicular fluid. It is currently standard practice in research to measure crevicular fluid flow by its electrical conductivity by means of a Periotron®; an invention by Canadians Israël Kleinberg, Lorne Golub, Samuel Borden, and Morris Settler. It was developed in the late 1960’s under a technology transfer grant to Harco Electronics from the federal government, which also supported Kleinberg’s antimony electrode that has been used widely for measuring plaque pH in response to carbohydrate challenge. Besides the measurement of flow rate, attention has been directed to analyzing crevicular fluid for specific mediators of inflammatory or destructive activity. Among these, there is considerable interest in the research of J. Sodek, C. Overall, and C. McCulloch, showing that matrix metalloproteinase activity in crevicular fluid and oral rinses can be used to discriminate between individuals with progressive periodontal attachment loss and those with non-progressing periodontitis, gingivitis, or healthy gingiva. Commercial applications are being investigated by Innova Corporation.

Over the past decade, the team down the hall from me has developed a Canadian innovation with the potential for making a huge impact on dental caries prevention. Chlorzoin®, the chlorhexidine-containing topical varnish system developed by H.J. Sandham and Thomas Balanyk, eliminates or greatly reduces mutans streptococcal infections better than any other reported agent. It is now licensed to Knowell Therapeutic Technologies, Inc., and it is already available to dentists in the Canadian marketplace. In the future, Chlorzoin® treatment might be applied as a prerequisite to the intentional implantation of non-cariogenic mutants streptococci to compete with the naturally acquired cariogenic phenotype. The idea for mutants replacement by LDH-deficient mutants was introduced and promulgated in the 1970’s and 1980’s by Jeff Hillman at Forsyth Dental Center. Yet Sandham’s lab has contributed highly significant advancements by engineering both LDH-defective mutants derived from a human isolate of Streptococcus mutans and the chemotherapeutic means to suppress the wild-type. Coincidentally, Chlorzoin® is currently sold in Canada along with Cariesscreen®, a mutants streptococci detection kit also developed at Forsyth.

The booming interest in osseointegration has led to several innovations in implant materials and designs. Adding to its reputation in implant dentistry attributable to George Zarb’s longitudinal research on applications of the Brånemark implant, Toronto has contributed two implants to
the Canadian marketplace. The Endopore® implant is the culminination of basic and applied research from an MRC Program Grant to investigators at the Faculty of Dentistry and Centre for Biomaterials Research: R. Pilliar, D. Deporter, Philip Watson, Michael Pharoah, J. Davies, D. Smith, and A.H. Melcher. The current ongoing program grant is directed to the biology of bone-implant interfaces. Human trials of the Endopore® implant are supported by Innova Corporation. The Ostial® implant was introduced this year, based on research by oral surgeons John Symington and Robin Listrom. It was developed with support from MRC-Industry and Innovations Ontario awards and partly from Knowell Technologies. The University of Montreal was recently awarded an MRC-Industry grant, under the direction of Jocelyne Feine, to study neurophysiological and patient-based outcomes of various designs for Nobelpharma implant-supported prostheses. Recently, Cameron Clokie and Dwayne Rahal of McGill, in partnership with Bristol Myers-Squibb, were awarded a Synergy Grant from the Province of Québec to study matrix augmentation by growth factors, like TGF-β, around tiny titanium implants in rodents.

**Economizing in the nineties**

Historically, MRC has recognized the specialized nature of dental research and, through training and development programs, has helped universities attract a cadre of well-trained principal investigators. However, as part of a renewed mandate with an eye on its budget, MRC has decided to terminate the Development Grant and the Dental Fellowship programs. It has also proposed changes to the peer review system that may lead to the termination of the Dental Sciences Committee, requiring grants from dental researchers to be reviewed by “peer” committees based on scientific discipline. Yet cariology is not cardiology. Whether non-life-threatening oral disorders will withstand the reviewers’ set of priorities remains to be tested.

The reality of shrinking public support has forced our granting agencies to fund few new grantees and to terminate or significantly cut budgets for many veterans. Compounding the dilemma is the paucity of industrial support for oral health research in this country of US subsidiaries. I fear that in this economic “re-adjustment” of the 1990’s, the promise of Canada’s budding international leadership in several fields of dental research will wither before reaching fruition. Yet I am entitled to express some typically mild Canadian optimism that the current situation will improve. After all, Canadians are known for dealing with a harsh climate!

Tough economic realities have also raised serious threats of closure for three of Canada’s faculties—Saskatchewan, McGill, and Alberta. Although there are community health reasons for these faculties to remain viable, it has been difficult for them to make compelling arguments that their research pursuits have met their universities' expectations. Survival in the 1990’s is a complex issue with many variables, especially budgetary. Yet back in his 1956 UBC prospectus and again in the 1986 MRC report, J.B. Macdonald bluntly forecast the plight of dental schools that did not concentrate their efforts in fundamental research:

“...Teaching without research is dead...No other investment can be expected to reap as rich dividends for the future as a well developed basic research program.” (Macdonald, 1956)

“...Leading schools tend to be agents of change, critics of conventional practice and exponents of reform and advancement...The professional schools which combine clinical excellence with genuine academic enquiry co-exist most comfortably with their parent universities...” (Macdonald et al., 1986)

His colleague Paynter said it this way:

“Dental faculties as part of universities are obliged to do research—it is part of their job...if [a faculty’s] objective is to perpetuate empiricism, it has no place in a university.” (Paynter, 1964)

**Accentuating the positive**

Canada is a country that often defines itself not by what it is but by what it is not. For example, its attitudes often fluctuate between that which is not American and that which is un-American, and therefore, the J Dent Res Editor broke the first rule of Canadiana by asking an emigré American to write about its history. In retrospect, this was perhaps a wise choice, since Canadians are not nurtured to be outwardly self-promotional. I doubt whether many of my Canadian Canadian colleagues would have been as bold to describe how fine their mark on dental research has really been...or would have boasted what a clever trade it was to get a periodontologist named Ellen in exchange for a Golub, a Listgarten, a Socransky, and a Taichman. Ask an average Canadian how s/he feels, and you get the answer, “Not bad, eh!” That’s exactly how we researchers in Canada feel about our historical contributions to international strengths in dental research: Not bad, eh!.....not bad at all!

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Dr. Ellen is Professor and Head, Department of Periodontics, University of Toronto, Faculty of Dentistry, 124 Edward Street, Toronto, ON, Canada M5G 1G6.