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Biomaterials in Canada: The first four decades

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Abstract

Biomaterials research in Canada began in the 1960s. Over the past four decades significant contributions have been made across a broad spectrum covering dental, orthopaedic, cardiovascular, neuro, and ocular biomaterials. Canadians have also been active in the derivative area of tissue engineering. Biomaterials laboratories are now established in universities and research institutes from coast to coast, supported mainly by funding from the Federal and Provincial Governments. The Canadian Biomaterials Society was formed in 1971 and has played an important role in the development of the field. The Society played host to the 5th World Biomaterials Congress in Toronto in 1996. The work of Canadian researchers over the past four decades is summarized briefly. It is concluded that biomaterials and tissue engineering is a mature, strong area of research in Canada and appears set to continue as such into the future.

Keywords: Canada; Dental biomaterials; Orthopaedic biomaterials; Cardiovascular biomaterials; Neuro biomaterials; Ocular biomaterials; Research funding in Canada; Canadian Biomaterials Society

1. Overview

Canada has had a presence in biomaterials since activity in this field began in the 1960s, and before the term was in general use. Over the past four decades Canadian scientists and engineers have made key contributions across the full spectrum of biomaterials research, including dental, orthopaedic, cardiovascular, neuro, and ocular biomaterials. Canadians have also been prominent in the related area of drug delivery and more recently in the derivative area of tissue engineering. The research covered in this article is restricted to biomaterials and tissue engineering. A brief account of this research over the past four decades is presented.

Activity has been at locations, mainly universities, across the country though with much of it in Ontario and Quebec, i.e. what is referred to as central Canada. The pioneering work of Dennis Smith and Walter Zingg, discussed in detail below, led to the major effort now ongoing at the University of Toronto. Of the 26 researchers whose work is discussed in this article, 10 are or were in Toronto, and several others were trained there. Biomaterials work is ongoing in a number of departments in both the medical and engineering faculties. A central focus is provided by the Institute of Biomaterials and Biomedical Engineering. In all, Toronto is one of the world's leading centres of biomaterials research. Another major centre in Ontario is at McMaster University in Hamilton. Activity has also developed over the last decade at Queen's University in Kingston, the University of Ottawa, and the University of Western Ontario in London.

In Quebec, the groups in Quebec City (l'Université Laval) and Montreal (l'Ecole Polytechnique and McGill University) have made many important contributions and these universities are today among the leading Canadian institutions doing biomaterials and tissue engineering research. The work at Laval is of long standing and dates back to the 1970s. Dalhousie University in Halifax has had activity since the 1970s also. This has recently been expanded with the

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establishment of the School of Biomedical Engineering which has biomaterials as one of its focus areas. In the West, work at the University of British Columbia, ongoing since the 1980s, and more recently at the University of Alberta, is noteworthy. The research achievements of the groups at all of these locations are described in some detail below.

It is always risky to pronounce judgement on specific research contributions. Such judgement clearly requires some historical perspective, and in this respect it is probably premature to judge more recent work. From the perspective of 2005, the following may be cited as among the major Canadian contributions:

- Polyacrylate bone cement and dental adhesives (Dennis Smith).
- Dental ceramics (Derek Jones).
- Porous metal coatings for joint prostheses (Robert Pilliar).
- Bone–material interface interactions (John Davies).
- Blood–material interactions and blood compatible materials (John Brash, Michael Sefton).
- Live cell encapsulation using synthetic polymers (Michael Sefton).
- Implant-patient interactions via device retrieval studies (Robert Guidoin).
- Contact guidance by topological micropatterning (Donald Brunette).

The international stature of Canadian biomaterials research has been recognized not only by the many publications of Canadian scientists in high impact journals, but also by the numerous awards received by these scientists. As one example, the Clemson Awards of the Society for Biomaterials (USA) have been given to six Canadian researchers. In addition a number of the prestigious Canada Research Chairs (CRCs) have been awarded to biomaterials/tissue engineering investigators, and several of our number are Fellows of the Royal Society of Canada.

As will be seen in the discussion below, biomaterials research in Canada is currently strong with a significant number of investigators at the beginning or mid-phase of their careers. The stage thus appears set for much important work to be accomplished well into the future.

2. The Canadian Biomaterials Society

On the initiative of Dennis Smith, Walter Zingg, and several others including Robert Jackson, Robert Salter, James Guillet, and Henry Garside, the Canadian Biomaterials Society was established in 1971. It is thus one of the first such societies in the world. The Society has held annual scientific and business meetings since 1972. The scientific meetings have become known and valued for their emphasis on student presentations and their informal ambience, with attendance typically in the 100–150 range. This relatively small size is compatible with a single session meeting where participants are exposed to all aspects of biomaterials. This is of course in contrast to the more typical larger scale meetings with their often "busy" atmosphere and multiple simultaneous sessions.

A major accomplishment of the Society was the hosting of the 5th World Biomaterials Congress in Toronto in 1996. Initially this was considered to be a risky undertaking for a relatively small group with limited financial resources. In the event, it was a highly successful meeting. Moreover a significant financial benefit accrued to the Society, and this has been invaluable in furthering the Society's goals. Toronto proved to be an excellent location, not least because of the high concentration of biomaterials activity in the Ontario region.

The Canadian Society has participated in the international cooperation initiatives among the Biomaterials Societies around the world. It was a member of the International Liaison Committee from its inception and is currently a member of the International Union of Societies for Biomaterials Science and Engineering.

3. Funding of biomaterials research in Canada

That biomaterials research in Canada has grown and prospered over the past four decades is due in no small measure to the availability of funding, the levels of which have grown considerably over the years. Most of the financial support has been provided by the Government of Canada. The Provincial Governments have also made significant contributions.

In the 1960s and 1970s, biomaterials research was funded principally by the Federal Government. The National Research Council of Canada (NRC) had a mandate to conduct research in its own laboratories across the country in the physical and biological sciences. It also had a granting function to provide funding for university-based research in these areas. In 1978 the university granting function was detached from the NRC and given to a new agency, the Natural Sciences and Engineering Research Council (NSERC), thus recognizing the increasing importance of providing support for research in the universities. At the present time NSERC provides funds to university researchers mainly through its "discovery" (formerly "operating", and later "research" grants), which allow researchers considerable latitude in pursuing their work. The NSERC discovery grants give modest but long-term, stable funding to researchers who remain productive. They have been a key factor in the success of the research enterprise in Canada. Other programs at

NSERC that have been of benefit to the biomaterials field have evolved over the years. These include the Strategic Grants, which are targeted to areas considered "strategic" for Canada. A currently targeted area relevant to biomaterials is "medical devices". The Collaborative Health Research Projects where physical scientists or engineers collaborate with biomedical scientists on health-related projects is a recent program that has been of benefit to biomaterials researchers. Most Canadian biomaterials researchers hold NSERC discovery grants and a number have been funded by the other programs as well.

The other major source of Federal Government support has been the Medical Research Council of Canada (MRC), which in 2001 became the Canadian Institutes of Health Research (CIHR) with an expanded mandate, but retaining the committee structure of the MRC through which much of the funding is allocated. The CIHR has a standing grants committee on Biomedical Engineering where investigator-initiated projects on medical imaging, biomechanics, and biomaterials (among other areas) are considered for funding. The Dental Science Committee as well as the Pharmaceutical Sciences Committee have also contributed to the funding of biomaterial-related areas. Through these committees the MRC/CIHR has been a major source of support for the biomaterials community in Canada for more than 30 years.

Two other Federal Government programs should be mentioned, namely the Canada Foundation for Innovation (CFI) and the CRCs. The CFI was set up in the late 1990s to facilitate the renewal of research infrastructure in Canada, targeting mainly the universities and hospitals. Infrastructure includes facilities, equipment, building renovations, and even new buildings. The CFI has had an enormous impact: new building has gone on at a brisk pace; many laboratories have undergone major facelifts and facilities upgrades. Again a significant number of biomaterials researchers have benefited from the CFI.

The CRC were designed to contribute to faculty renewal in the face of a wave of retirements in the 1990s and beyond and declining university budgets (a provincial responsibility under the Canadian system). Funding was provided for 2000 positions allocated to each university on the basis of its historical research performance. Clearly this has given a tremendous boost to the Canadian academic enterprise and to research in particular. A number of these Chairs have been awarded to individuals working in biomaterials and tissue engineering.

At the provincial level, research funding has also been significant. In Ontario, the Centres of Excellence were introduced in the late 1980s, among them the Ontario Centre for Materials Research (OCMR). This Centre had a number of thrust areas including biomaterials, and provided significant funding for research projects across the spectrum from blood-contacting to dental biomaterials. It also made a major contribution to the establishment of the Centre for Biomaterials at the University of Toronto, providing funding, for example, for an XPS facility dedicated to biomaterials. More recently the Ontario Centres have been restructured. Biomaterials is now funded through Materials and Manufacturing Ontario, with an increased emphasis on translation and commercialization aspects generally. In Québec, biomedical research has been funded through the Fonds de la Recherche en Santé du Québec (FRSQ), the Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (FCAR), and its successor the Fonds Québecois de la Recherche sur la Nature et les Technologies. In Alberta, the Alberta Heritage Foundation for Medical Research (AHFMR) has provided some support for biomaterials research, and the recently formed Alberta Ingenuity Fund (AIF) has made significant investments in several emerging research laboratories associated with biomaterials, particularly at the University of Calgary.

Non-government research foundations, for example the national and provincial Heart and Stroke Foundations, have also contributed significantly to the funding of the Canadian biomaterials research effort.

4. The "players" and their contributions

In this section, I have attempted to highlight the contributions of various laboratories and investigators across the country. I believe I have included most of the significant Canadian work over the past 40 years. Inevitably, however, mainly through ignorance, I will have omitted work that deserves to be discussed. To the researchers whose work falls into this category I offer my apologies.

The text is arranged chronologically so that the work of researchers is discussed based on the decade in which they became active and/or in which their work began to have impact. This is not the only way in which the material could be organized, but it does give a sense of the development and growth of Canadian efforts over the years. Growth has been continuous and at times, e.g. the past five or so years, extremely rapid. With the advent of tissue engineering as a new major area of application of biomaterials, it appears that such rapid growth will continue into the future.

4.1. 1960s: the seed is sown

The first significant Canadian work was that of Dennis Smith in dental materials and Walter Zingg in cardiovascular materials. These two individuals should be given credit not only as the first researchers in

Canada to devote their careers to biomaterials, but also as pioneer builders and promoters of the biomaterials enterprise in this country.

Dennis Smith may fairly be described as the "father" of biomaterials in Canada. His achievements are remarkable in several respects: scientifically, administratively, and in terms of service to the broader biomaterials community. After a successful career in the UK, where he established the Department of Dental Materials at the University of Manchester, he came to the University of Toronto in 1969. There he set up the Biomaterials Department in the School of Dentistry. The Centre for Biomaterials was established some years later (1986) with strong links to many other Departments and to other Canadian Universities. As mentioned above, Dennis was the prime mover in establishing the Canadian Biomaterials Society in 1971. He retired formally in 1993 but remains active in research and other aspects of biomaterials work; for example he is currently the Chair of ISO/TC106-Dentistry (1999–2005).

In research Dennis has had a huge impact with work in a number of areas, but above all, in dental biomaterials. He has pointed out that biomaterials as we now know it owes much to the study of dental materials which predated the broader biomaterials field. Among his achievements in the dental area are the invention of the polyacrylate adhesive cements [1] and contributions to the development of other adhesive dental materials [2]. In orthopaedics, he was responsible with John Charnley for the development of acrylic bone cement in the period 1957–1973 [3]. In this connection it should be noted that the Proceedings of a Symposium on Bone Cement, which has an account of the genesis of bone cement, was published recently in Orthopaedic Clinics of North America [4]. Most recently he has been involved in a series of pioneering studies (with Walter Peters) on the influence of silicon and silicones on the clinical response to breast implants (1992–2001) [5].

Walter Zingg, who had a long career at the University of Toronto and the Toronto Hospital for Sick Children, was the first Canadian practitioner (and booster) of biomaterials to come from a medical background. Walter was a surgeon by original training and had interests in hypothermia associated with heart–lung bypass. The first Zingg paper with a clear biomaterials connection was published in 1960 [6]. In this paper, he reported on the use of a commercial polyurethane for the repair of bone fractures and commented on its lack of tissue reaction, a finding that was to be repeated many times in the years that followed. Walter also worked briefly on blood rheology [7].

These interests led him to collaborations with engineering colleagues Charles Ward and Wilhelm Neumann, and somewhat later with Michael Albisser and Michael Sefton. With Ward he worked on the role of gas microbubbles on blood–material interactions with a clear connection to blood oxygenators [8]. With Neumann over a period of about 15 years (1975–1990) he worked on surface thermodynamics approaches to the study of blood–material interactions [9,10]. This work was highly productive and served to focus attention on the importance of fundamental surface science and the use of simple measurements such as contact angle.

Walter's collaboration with Sefton was also productive and covered the range from cardiovascular materials [11,12] to insulin pumps [13]. Walter's contributions were mainly in the development of animal models for evaluation of materials and devices. The A–V shunt dog model for blood compatibility testing, for example, has generated much valuable information [11].

4.2. 1970s: the plant takes root

In the 1970s the level of activity increased significantly with the arrival on the scene of Robert Guidoin (Université Laval), Derek Jones (Dalhousie University), Robert Pilliar (University of Toronto), Michael Sefton (University of Toronto), and John Brash (McMaster University). Guidoin, Sefton, and Brash were interested mainly in blood contacting materials and have continued to work in this area up to the present time. Pilliar has made seminal contributions to orthopaedic biomaterials and devices, and Jones in the dental biomaterials area.

John Brash joined McMaster University in 1972. Over the years his laboratory has worked extensively on the fundamentals of blood–material interactions [14–17]. They were among the first to point out the primordial nature of protein adsorption in all biomaterials applications and to make the connection between protein adsorption and cell adhesion. They have also contributed significantly in the development of biomedical polyurethanes [18,19]. More recently they have worked on anti-fouling surfaces based predominantly on polyethylene oxide. They have advanced the idea of achieving biocompatibility by combining suppression of non-specific interactions and promotion of specific interactions [20]. An example of the latter is the promotion of endogenous plasminogen and t-PA adsorption from blood to potentiate the dissolution of nascent clots [21].

Michael Sefton has worked on biomaterials and related areas at the University of Toronto since 1974. His laboratory has produced a large body of work on the development and understanding of heparinized materials for blood contact [22,23]. Other blood-related work includes the development of a chronic animal model for the evaluation of blood compatibility [11], extensive studies of complement activation which drew attention to the role of the classical pathway in biomaterial-complement interactions, and adaptation of fluorescent activated flow cytometry to study platelet and leukocyte activation [24].

More recently the Sefton laboratory has made pioneering contributions to tissue engineering, with a focus on cell encapsulation using copolymers of HEMA and MMA among others [25]. They were one of the first laboratories to succeed in encapsulating live cells while maintaining cell viability. A variety of cell types have been encapsulated [26] and the products of this work are expected to have a significant impact in areas such as diabetes, Parkinson's disease, and gene therapy.

Since the mid-1970s at l'Université Laval in Quebec City, Robert Guidoin's laboratory has contributed extensively to knowledge of the behaviour of vascular implant devices clinically through retrieval studies [27]. They have also worked on the development of membrane oxygenators [28], and blood conduits of various kinds including polyester grafts impregnated with bioerodible scaffolds as an alternative to preclotting [29], chemically treated biological grafts (human umbilical cord vein) [30], and cryopreservation of veins as arterial conduits (homografts) [31]. Other contributions have been in the breast implant area, e.g. the identification of hopeite and parascholzite in the mineralization of these implants [32], and more recently the development of the concept of virtual biopsies for non-metallic implants by means of MRI [33].

Robert Pilliar is widely recognized as a pioneer in biomaterials for orthopaedic applications, working since the early 1970s at the Ontario Research Foundation and later at the University of Toronto. He was responsible for the development of orthopaedic implants (hip replacements primarily in the early days) designed with porous coatings that gave structures suitable for bone ingrowth resulting in three-dimensional interlock of implant with bone [34]. This work resulted in a patent that subsequently was licensed by a major orthopaedic implant manufacturer. Later studies drew attention to the loss of bone due to stress shielding in well-fixed implants and to the importance of initial implant stability and lack of relative movement at the implant-bone interface to allow bone ingrowth rather than fibrous tissue attachment [35–37]. In the 1980s, the porous coating concept was extended to dental implants [38]. This work resulted in the development of a porous-surfaced Ti alloy implant system that was licensed to Innova Corp., later Innova LifeSciences that has manufactured and marketed the novel implant worldwide. Most recently novel porous biodegradable inorganic structures suitable for tissue engineering applications in joint replacement have been developed [39]. These structures rely on soft tissue ingrowth (articular cartilage, nucleus pulposus) into porous bone-interfacing structures that can then be stabilized in vivo through bone ingrowth into the bone interfacing portions of the implants. It is of interest also to note that in the 1980s, studies on the use of porous-coated surfaces demonstrated their effectiveness in cardiac pacing devices and in the metallic (titanium) components of LVADs.

Derek Jones is one of the pioneers worldwide in dental biomaterials. He arrived at Dalhousie University from England in 1975. There he set up a Division of Biomaterials and an active research laboratory. His initial research was in the area of silica chemistry, the characterization of ceramics, and the diffusion of plasticizers in polymer systems [40,41]. He also worked extensively on the synthesis of ceramic and glass materials including oxide glasses (poly component ion leachable glasses) by wet chemistry [42], and studies of the influence of fillers on the mechanical properties of polymer–ceramic/glass composite materials [43]. A notable aspect of Derek's work was his defence of the scientific principles associated with the use of dental amalgam as a restorative material [44].

Paul Wang was also among the early Canadian biomaterials researchers. At the University of Toronto he worked on tissue adhesives and showed that adhesives based on synthetic polymers can adhere well to wet biological tissues after priming with benzoyl chloride [45]. In later work he developed a sustained release insulin implant [46] which was commercialized (trademarked Linplant) and has been used primarily in treating diabetic research animals.

The work of Irwin Feuerstein (McMaster University) on blood cell–surface interactions, particularly platelet interactions, was initiated in the 1970s. His approach to blood–surface interactions emphasized the role of haemodynamics as well as the interface itself [47]. Considerable insights were gained with the introduction of videomicroscopy methods for the visualization of platelet interactions in whole blood [48,49]. Later work was concerned with the morphology of adherent platelets, and with the interactions of platelets and proteins at surfaces [50].

4.3. 1980s: the plant flourishes

This decade saw expansion of activity in the orthopaedic and cardiovascular areas as well as the beginnings of tissue engineering (though the latter term did not come into general use until the 1990s). Among Canadian investigators beginning their work in this period were John Davies (University of Toronto), Michael Lee (University of Toronto), Don Brunette (University of British Columbia), Charles Doillon (l'Université Laval), Francois Auger (l'Université Laval), Lucie Germain (l'Université Laval), and Dennis Bobyn (McGill University).

Initially in the UK and since the late 1980s at the University of Toronto, John Davies has made seminal contributions to the understanding of interactions at the bone–material interface and to bone tissue engineering [51]. He is responsible for two key publications in this area: The Bone–Biomaterial Interface, published in 1991 [52], and Bone Engineering, published in 2000 [53].

Michael Lee, first at the University of Toronto and more recently at Dalhousie University in Halifax, Nova Scotia, has pursued work on the mechanical properties of vascular tissue and its components, with important implications for the development of bioprosthetic heart valves and blood vessels. Lee's laboratory showed that high strain rate testing is necessary to accurately describe the viscoelastic function of cardiac tissues such as the pericardium and heart valve leaflets [54]. They have also worked extensively on collagen crosslinking as it relates to bioprosthesis processing, including studies of novel tissue processing techniques and new methods for mechanical and thermomechanical testing [55,56]. Recently they have demonstrated synergies between fatigue damage, dynamic loading, and enzymolysis in the failure of bioprosthetic vascular tissue [57].

Charles Doillon, with formal training both as a physician and a researcher, is one of the first Canadian workers to have had an impact in tissue engineering. Working in Quebec City at l'Université Laval, his major contributions are in wound healing and tissue replacement by collagen-based materials (e.g., wound dressings), and more recently, in tissue engineered cornea and the problem of angiogenesis in biomaterials. An important idea was to combine growth factors with reconstituted extracellular matrices (ECM), thus mimicking more closely the natural tissue environment. It was found that fibrin is successful in maintaining growth factor activity in vitro and in vivo and is a suitable matrix in collagen-based materials. This idea was applied to endothelial cell linings and wound scaffolds using autologous fibrin [58]. In collaboration with May Griffith (University of Ottawa), the Doillon laboratory also contributed to the design of an artificial cornea/sclera by developing two interpenetrating 3-D systems [59]. The most recent work has been devoted to the problem of angiogenesis and vasculogenesis, with the objective of enhancing blood supply in tissue engineered scaffolds and wound tissues [60,61].

François Auger, also at l'Université Laval, is among the foremost of the pioneers in tissue engineering, particularly in the areas of skin and vascular applications. As a physician researcher he established the Laboratoire d'Organogénèse Expérimentale (LOEX) at Laval in the mid-1980s. Cell biologist Lucie Germain joined the group soon after. She holds the Canada Research Chair in Stem Cell and Tissue Engineering. These two investigators have developed a new and original approach to tissue engineering, viz. the self-assembly method [62]. This method uses the intrinsic capacity of cells to synthesize and organize their extracellular matrix as a "physiological biomaterial" (without any synthetic component), which then self-assembles into organized tissue substitutes. Using this approach they have been responsible for several key developments in tissue engineering using only human cells: the first totally biological vascular substitute [63], the first capillary system in an organ substitute [63], and the first corneal substitute from primary cultures of normal cells [64,65]. They have also published on skin stem cells [66], and an in vitro model of wound healing [67].

Cell biologist Don Brunette and his group, working at the University of British Columbia, have pioneered an approach that draws attention to the effects of surface topography on cell behaviour. They have adapted techniques developed for the production of microelectronics to fabricate precisely controlled surfaces for the study of cell–surface behaviour [68]. Using this approach, studies on the mechanism of contact guidance on microfabricated surfaces were carried out. Initial studies examined the behaviour of fibroblasts, and showed that these cells responded hierarchically to surface topographic cues [69]. Later work investigated the role of the cytoskeleton in cells exhibiting contact guidance [70]. This group has extended these ideas to the in vivo situation and has shown that contact guidance occurs in vivo as well as in vitro [71]. The work of Brunette has broad implications for the design of implants in many anatomic locations including dental tissue, soft tissue, and bone.

Dennis Bobyn has worked for the past 25 years on orthopaedic biomaterials. His work has focused on a broad range of issues, including tissue response to implant materials with different surface characteristics [72], retrieval analysis of human joint replacement prostheses [73], bone remodelling studies of hip prostheses with various fixation and stiffness properties [74], and studies of the wear and lubrication of metal–metal hip bearings [75].

4.4. 1990s: the plant grows rapidly, a hybrid takes root

Biomaterials in Canada continued to grow in the 1990s with the emergence of new laboratories in Toronto, Montreal, London, Quebec City, Edmonton, Ottawa, and Halifax. New investigators coming into the field in this period were Michael Buschmann (Ecole Polytechnique, Montreal), Gaetan Laroche (l'Université Laval), Paul Santerre (University of Toronto), Molly Shoichet (University of Toronto), Wan K. Wan (University of Western Ontario), Kim Woodhouse (University of Toronto), L'Hocine Yahia (Ecole Polytechnique, Montreal), Hasan Uludag (University of Alberta), May Griffith (University of Ottawa), and Mark Filiaggi (Dalhousie University).

Michael Buschmann, at l'Ecole Polytechnique in Montreal, holds the Canada Research Chair in Cartilage Tissue Engineering. His work focuses on the biology and biomechanics of articular cartilage and the meniscus, and on the use of natural polysaccharides for tissue repair, with particular emphasis on chitosan [76]. His laboratory has found that mixtures of chitosan with blood components give hybrid biomaterials that have the capability to stimulate repair of articular cartilage lesions by recruiting host cells from adjacent regions. A Canadian company, BioSyntech, owns this technology and is running a clinical trial to establish efficacy in humans.

The work of Gaetan Laroche at Laval is in the cardiovascular area. Besides his investigations of explanted prostheses in collaboration with Robert Guidoin, he has done work on modelling the uptake of lipids by arterial prostheses [77,78]. He has also contributed to the science and technology of biomaterial surface modification by cold plasma methods. This work includes chemical functionalization and attachment of bioactive molecules [79,80].

Diego Mantovani, also at Laval, has worked on metallic alloys for a new class of degradable coronary stents [81]. Other work is on solid coatings with carriers for the attachment of bioactive molecules to the surface of metallic stents [82], and on new strategies to trigger the signalling mechanisms between the inert surface of a prosthesis and the living environment surrounding the implanted arterial prosthesis [83].

Paul Santerre, first at the Ottawa Heart Institute and then at the University of Toronto, has worked on enzyme, protein, and cellular interactions with surfaces. He has collaborated extensively with Rosalind Labow (University of Ottawa) in this work. A major theme has been the biostability and biodegradation mechanisms in segmented polyurethanes, a class of materials that have been used extensively in blood contacting devices [84]. Mechanisms of degradation of dental composites used in restorative dentistry have also been clarified: this work showed that these materials are degraded by salivary esterase [85]. This group has also developed a number of materials based on the idea of blending surface-active agents with a "base" material, e.g. polyurethane. The agent migrates to the material–tissue interface and provides appropriate bioactivity or bioinertness. One example is the use of fluorinated agents that have been shown to reduce platelet reactivity in blood contact [86]. This approach has led to the formation of a spin-off company Interface Biologics, focused on a second generation of surface modifiers that can deliver biological agents, e.g. anti-proliferative and anti-coagulant drugs, to surfaces.

Molly Shoichet at the University of Toronto holds the Canada Research Chair in tissue engineering. Her laboratory is unique in Canada in its focus on neurobiomaterials and tissue engineering. Their contributions have been in materials for nerve guidance and guided regeneration. They showed how photochemistry and laser technology could be used to create longitudinal, cylindrical volumes of peptides to guide the growth and movement of cells and neurites [87]. In other work they have demonstrated that a minimum linear concentration gradient of neurotrophic factors is required for neurite guidance [88], and that this minimum decreases when multiple factors are used together due to synergism in cell receptor response [89]. With respect to device design, a method has been developed to fabricate tubes based on poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) [90]. These were tested for their regenerative capacity as nerve guidance channels in both the transected peripheral nerve [91] and spinal cord [92].

A new locus of Canadian biomaterials activity is the laboratory of Wan K. Wan at the University of Western Ontario in London. Their work focuses on both biostable and biodegradable materials depending on the targeted application. Biostable materials such as PVA and PVA-microbial cellulose nanocomposites have been developed for use in long-term replacement implants such as cardiac valves [93,94]. Biodegradable materials are also being developed for degradable implants and tissue engineering. Mechanical modelling and computer simulation are also an integral part of their research in the design of medical devices.

Kim Woodhouse has established a laboratory at the University of Toronto focused primarily on tissue engineering for vascular applications. The major contributions of this group have been in the development of tissue engineering scaffolds based on synthetic and natural polymers. They have developed biodegradable polyurethanes based on amino acid chain extenders [95]. These are being evaluated for use in cardiac patching [96]. They have also worked on a human recombinant elastin-like polypeptide that has shown potential as a non-thrombogenic coating and scaffold [97]. This work has resulted in the formation of the start-up company Elastin Specialties (ESI) producing peptides derived from human elastin with applications as coatings, stand-alone biomaterials, and scaffolds for tissue regeneration and growth.

At l'Ecole Polytechnique in Montreal, the work of L'Hocine Yahia is biomechanics oriented. This group has contributed to the understanding of loosening at the bone–implant interface. They showed that osteolysis leading to aseptic loosening is related to the nature of wear particles that are formed [98], and that ceramic and polyethylene particles induce macrophage apoptosis [99]. Their work led to the hypothesis that some failures are related more to mechanical factors (mismatch of both elastic modulus and damping capacity) inducing apoptotic cell death rather than to the cytotoxicity of wear particles. Porous nickel–titanium (NiTi) was introduced to reduce stiffness and increase shock absorption capacity at the bone–implant interface [100]. They have also worked on porous natural coral as a scaffold material for bone tissue engineering (bone graft substitute) [101], involving seeding with osteoblasts and release of growth factors [102]. The biocompatibility and corrosion properties of the shape memory alloy NiTi, e.g. as a vascular stent material, have been investigated extensively by this group [103].

Hasan Uludag spent several years in industry before joining the University of Alberta in Edmonton. His work is in bone tissue engineering and drug delivery. In the bone area, he has worked on designing biomaterials to control the in situ residence time of morphogens (e.g. bone morphogenetic protein-2) for bone induction [104]. His drug delivery work is on targeting systemically administered growth factors to bone based on conjugating the growth factors with bone-seeking bisphosphonates [105].

At the University of Ottawa, May Griffith works on tissue engineering with a focus on functional replacements for extracellular matrix that will promote tissue regeneration. Using biological polymers as starting materials, she developed a functional tissue equivalent to human corneal tissue for in vitro toxicology testing [59], which was subsequently innervated to increase functionality [106]. More recently, her group has developed a corneal substitute that is a hybrid of collagen and synthetic polymers [107]. This material can be moulded to the curvature and dimensions of a human cornea, with optical clarity and adequate mechanical strength for suturing. When transplanted into animals, these materials allowed regeneration of corneal cells and nerves that were removed during the surgery.

Mark Filiaggi, presently at Dalhousie University, has made significant contributions in bioceramics, particularly in the area of materials processing. His early work was on materials processing and strength aspects of plasma-sprayed hydroxyapatite coatings on metallic implants [108]. Most recently he has worked on a calcium polyphosphate degradable ceramic that is currently the basis for joint re-surfacing applications [109], and on calcium phosphates as therapeutic delivery agents in bone tissue engineering and bone-interfacing applications [110].

4.5. Into the 21st century

The present decade has seen the emergence of a new generation of investigators including Paul Gratzer, Heather Sheardown, Maryam Tabrizian, Patrick Vermette, Ze Zhang, and Rizhi Wang. The work of this group covers the gamut from blood to soft tissue to bone, and from "traditional" applications to tissue engineering. They have already made significant impact and will undoubtedly ensure the continued progress and excellent quality of biomaterials research in Canada into the future.

The work of Paul Gratzer at Dalhousie University is mainly on tissue-derived biomaterials and related tissue mechanics. Examples are work on the enzymatic solubilization of collagen by chemical modification of amino acid side-chains [111], and on the decellularization of allograft anterior cruciate ligament (ACL) tissue to create a scaffold for cellular repopulation [112].

At McMaster University, Heather Sheardown works on ophthalmic biomaterials. Materials for applications in the anterior segment of the eye are being developed, e.g. interpenetrating networks of poly(dimethyl siloxane) and a hydrogel [113]. Surfaces that support corneal epithelial cell adhesion and growth are also under development, for example using cell adhesion peptides and growth factors [114]. Other work is aimed at creating protein-resistant and bioactive silicone polymers by tethering polyethylene glycol [115], and molecules such as heparin, growth factors, and cell adhesion promoters.

Maryam Tabrizian has established a biomaterials laboratory at McGill University. She has worked extensively on surface treatment to improve biocompatibility with strong emphasis on sterilization issues [116], and on blood compatibility, e.g. strategies to inhibit restenosis in coronary stents [117]. She has also initiated a program on biorecognition and biosensors for real-time monitoring [118].

Patrick Vermette has recently joined the University of Sherbrooke. He has worked extensively on materials prepared by the immobilization of liposomes on solid surfaces. These materials are designed for use in site-specific drug delivery or in tissue engineered materials [119,120]. One example of the former is in contact lenses. This group has also recently published a monograph on biomedical polyurethanes [121].

Ze Zhang, one of the newer members of the group at Laval, has worked on electrically conductive biodegradable polymer composites for tissue engineering. The idea is to allow electrical stimulation of constructs via a conductive and largely biodegradable scaffold [122]. The conductive composite contains only about 5% of the conductive component polypyrrole, the rest consisting of biodegradable polymers such as polylactide. He has also contributed to studies of Vascugraft, the first poly(carbonate urethane) vascular prosthesis [123].

Rizhi Wang is a recent faculty member at the University of British Columbia and is the holder of the Canada Research Chair in Biomaterials. His research is concerned with bone fracture, biological interfaces, and processing of multifunctional biomaterials. He has developed a technique for studying the strain redistribution that occurs during bone deformation, and is working towards monitoring femoral fracture at both macroscopic and microscopic levels.

In the biomaterials processing area, he is developing materials and techniques for improving the bioactivity of orthopaedic implants [124]. An example is the bioceramic coating on metallic implants that can deliver anti-inflammation and anti-osteolysis drugs [125].

5. Conclusion

From the above discussion it is clear that biomaterials and tissue engineering is a strong area of research in Canada. Work across the spectrum from fundamental to applied is represented. The enterprise is vigorous and mature, though young enough that most of those who entered the field since its beginnings are still active. Many of the laboratories whose work is discussed above are represented in the collection of papers that constitutes this special issue. In these papers readers will find compelling evidence of the impressive breadth and depth of biomaterials research in Canada.

Acknowledgments

I thought it wise not to rely too much on my personal perceptions of the work of the various laboratories. Accordingly I solicited input from the investigators. The response was excellent and for that I am grateful: a good deal of the text is based on this input. Where descriptors such as "significant", "seminal", "pioneering" and the like are used they reflect my personal opinions.

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