DISCOVERY!
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Discovering the Impact of Ronald Gibbons on Dental Research and Beyond

There should be a way to search PubMed to find the Impact Factor (IF) for an individual investigator. If there were an IF for ranking researchers, the late Ronald J. Gibbons ['Ron' to all who knew him] would be the standard, arguably the top-ranked IF of his generation in dental research. Ron Gibbons' legacy is huge in cariology and periodontal research, and way beyond in the fields of anaerobic bacteriology, microbial ecology, bacterial adhesion, and local immunity. A search of MEDLINE spanning the late 1950s to the early 1990s, an era of paper and postal communication that was unimaginably slow by today's broadband standards, would find a great number and incredibly wide range of cutting-edge Gibbons publications that infused our field with novel ideas (Table 1). Yet, a true IF for an investigator should also consider his/her IF as a mentor, the legacy of the teacher, role model, and motivator who populates the research community with a generation of trainees who go on to attain a high IF in their own right (Table 2). We three clinician-scientists of relatively modest IF, who drove our research in distinct directions in three different countries, join together in this "Discovery!" to help the readers of the *JDR* discover the remarkable international impact of our mentor, Ron Gibbons, in and beyond the field of fundamental oral microbiology.

THE EMERGING YOUNG INVESTIGATOR OF THE 1960s

Ron Gibbons, like his contemporary, microbiologist Ed Moore of Virginia Polytechnic Institute, who died the same September, 1996, was trained as a rumen microbiologist, whose lab animal of choice was the cow (Gibbons *et al.*, 1955). This is relevant for grasping Ron's swift contributions upon his recruitment at the dawn of the 1960s to the Forsyth Dental Infirmary (later Forsyth Dental Center, today The Forsyth Institute), Boston. Rumenologists had just solved a major puzzle: how ruminants survived by digesting cellulose, when neither the ruminant nor any cultivable bacterium isolated from rumen contents expressed cellulase activity. The answer was simple. If the rumen specimens were cultured by the strictest of anaerobic techniques (recently developed by R.E. Hungate), almost all isolates possessed cellulase activity. The dominant anaerobic flora in the rumen had been overlooked. Though Ron did not introduce Hungate's roll-tube technique to oral microbiology, as did Peg Holdeman (later Moore) and Ed Moore, he did bring the knowledge that anaerobes not only dominated on the mucous membranes, but also greatly outnumbered the aerobic flora. This information led to studies on the predominant cultivable flora of supra- and subgingival plaque, tongue, and saliva that laid the foundation for our current understanding of oral microbial ecology, and subsequent unraveling of the complex microbial etiology of dental caries and periodontal diseases.

These studies established that there were distinct microbial communities in the oral cavity, *i.e.*, the flora of the supragingival plaque was different from that of the subgingival plaque, and that neither plaque contributed significantly to the flora of saliva. The salivary flora was primarily representative of the tongue, explaining why *Streptococcus salivarius,* the dominant streptococcus in the saliva, could hardly be found on the teeth. The dominant organisms in the supragingival plaque were streptococci identified at the time as *Streptococcus sanguis* and *Streptococcus mitis,* and oddly shaped rods called 'diphtheroids', which Ron helped to identify. The dominant organisms in the subgingival plaque were mainly Gram-negative rods suspected to be bacteroides and fusobacteria.

Ron had been hired in 1960 by Forsyth Director John B. ['Jack'] Macdonald to work with him and with Sigmund Socransky, one of Jack's former students from Toronto. Together, they continued to exploit a mixed-anaerobic infection model in the guinea pig in which reproducible abscesses could be transmitted by a finite number of oral species, including a black-pigmented bacteroides, known then as *Bacteroides melaninogenicus*. Though *B. melaninogenicus* was the key member of the group, its presence depended on nutrients provided by the other organisms. These nutrients were shown to be hemin and menadione (vitamin K) for *B. melaninogenicus* (the pathogenic type is now known as *Porphyromonas gingivalis*) and became the focus of one of Gibbons' publications in *Science.* Growing from this series of studies, Gibbons, Socransky, and Walter Loesche, Ron's first PhD student, standardized laboratory cultivation methods for several types of oral anaerobes.

These observations on microbial interactions indicated that bacterial synergisms were an important ecological determinant for the flora found on mucous membranes. In the 1950s,

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Table 1. Discovery!—Novel Ideas and Advances Introduced by R.J. Gibbons*

- Bacteroides melaninogenicus produces enzymes with collagenolytic activity (Gibbons and Macdonald, 1961)
- *B. melaninogenicus* requires hemin and menadione for growth; other anaerobic species supply menadione, vitamin K (Gibbons and Macdonald, 1960; Gibbons and Engle, 1964)
- Pigmented anaerobes are required in abscess-forming mixed-anaerobic infections (Macdonald *et al.*, 1963; Socransky and Gibbons, 1965)
- Oral bacteria store intracellular polysaccharides as a future carbohydrate source, a potential cariogenic trait (Gibbons and Socransky, 1962)
- Practical identification of oral Gram-negative anaerobic rods (Loesche and Gibbons, 1965)
- *S. mutans* cells adhere to teeth and to each other *via* glucans synthesized by "dextran sucrases" (glucosyl transferases), with sucrose as the natural substrate (Gibbons and Banghart, 1967)
- Bacteriocins (antibacterial peptides) synthesized by some oral streptococci and targeted at others may affect the local microbial composition of dental plaque (Kelstrup and Gibbons, 1969; Kelstrup *et al.*, 1970)
- Interbacterial aggregation (now "co-aggregation" or "co-adhesion") is an important mechanism in the formation of dental plaque (Gibbons and Nygaard, 1970)
- The specificity of adhesion is an ecological determinant for the establishment and distribution of bacteria on oral surfaces bathed by secretions (Gibbons and van Houte, 1971; Liljemark and Gibbons, 1971)
- Adhesion specificity is a prerequisite for the expression of virulence of extra-oral pathogens, due to its impact on their initial colonization and tissue tropisms (Ellen and Gibbons, 1972)
- The disaccharide sucrose can be transported intact by *S. mutans* and metabolized intracellularly (Gibbons, 1972)
- The function of secretory IgA is to inhibit bacterial adhesion to bathed surfaces (Williams and Gibbons, 1972)
- Some salivary glycoproteins function to inhibit bacterial adhesion to oral mucosa (Williams and Gibbons, 1975)
- Adhesion specificity determines the host range of parasitic micro-organisms (Gibbons *et al.*, 1976a)
- Oral bacteria adhere selectively *via* stereochemical interactions, including their surface lectins that recognize cognate carbohydrate sequences on oral glycoprotein receptors (Gibbons and Qureshi, 1978; Gibbons *et al.*, 1985)
- The affinity of bacteria and the number of binding sites (valency) can be determined by applying (Langmuir) isotherms used for the study of molecular interactions (Gibbons *et al.*, 1976b, Clark *et al.*, 1978)
- Since teeth are its primary reservoir, *S. mutans* can be eliminated from the mouth by short-term, intensive antiseptic therapy (Caufield and Gibbons, 1979)
- Proline-rich proteins and statherin are important bacterial ligands in salivary pellicle (Gibbons *et al.*, 1988)
- Bacteria have evolved to adhere *via* "cryptitopes", cryptic receptors on host surfaces that may be exposed by conformational change or enzymatic modification (Gibbons *et al.*, 1990)

* Conceptual leaps and major findings articulated by Ronald J. Gibbons, his trainees, and collaborators that opened new research territory and led to sustained activity by others.

Reyniers had developed the germ-free isolator that allowed certain rodents to breed in a microbe-free environment. Macdonald's group saw the germ-free animal as an important tool for the elucidation of the role that these microbial interactions played in oral ecology. They developed a germ-free rat colony that helped prove the cariogenicity and periodontal pathogenicity of individual species. The facility served the dental research community for the next 25 years.

In the early 1960s, Paul Keyes and Robert Fitzgerald of the National Institutes of Health in the USA showed that dental decay was a transmissible infection in the hamster, and that only certain streptococci were cariogenic in germ-free rats. Then, in Sweden, Bo Krasse showed that the 'cariogenic streptococcus', *Streptococcus mutans*, was unique in its dependence upon sucrose to cause decay in hamsters. While collaborating with Keyes and Fitzgerald, Ron Gibbons was among the first to notice that *S. mutans* adhered to the walls of the culture tube when grown in sucrose broth. It was known in the sugar industry that certain bacteria could form a glucose homopolymer, dextran, from sucrose. Ron then showed that dextran was formed by *S. mutans*. Yet, soluble dextran could be degraded by some plaque bacteria, and the thinking at the time was that it may serve as an extracellular reserve carbohydrate source, much like the intracellular glycogen-like polysaccharides that Ron and his co-workers had previously found in many species of oral bacteria (another lead from his rumen microbiology days!). Notably, *S. mutans* also synthesized insoluble glucans; these branched polymers were identified and termed 'mutan' by Bernie Guggenheim in Switzerland.

The mid-'60s were watershed years for cariology, and Ron Gibbons' seminal reports—that glucan-mediated adhesion promoted plaque formation and caries by *S. mutans*—helped launch the next few decades of research on glucans, glucan-synthesizing glucosyl transferases, and caries vaccines based on either these enzymes or glucan-binding proteins. His pioneering work was recognized internationally, when he received the IADR's Basic Research in Oral Science Award in 1967 and the Distinguished Scientist Award in Cariology in 1990, and nationally with NIDR's Kreshover Lecture in 1989 (Gibbons, 1989). The role of glucan-mediated adhesion by *S. mutans* in colonization was the spark for the huge thrust on the ecology of oral streptococci that Ron and his colleague Johannes van Houte would drive into the 1970s. Their idea—that bacteria evolved specific mechanisms to recognize receptors on mucosal or salivary pellicle-coated surfaces, and that the differential ability of fostered microbial

colonization to adhere at distinct locations in the mouth—was a straightforward, fundamental hypothesis that was to bring much clarity and promise to the fields of infection and immunity...a 'Eureka!' moment, indeed.

LEADING THE BOOM IN BACTERIAL ADHESION RESEARCH, STILL IN HIS 30s AND EARLY 40s

1970 saw the launch of a new journal, *Infection and Immunity*. Gibbons and van Houte jumped in with a 1971 publication that expanded their concepts of adhesion and its effect on bacterial colonization of oral mucosal surfaces exposed to a fluid flow. The paper made the list of the decade's most frequently cited works in all the biomedical literature. The discovery was fresh, the data supportive, and the authors showed an uncanny ability to communicate their ideas to a general audience in this and a follow-up paper, with post-doctoral fellow Bill Liljemark, on the adhesion of additional oral genera. Ron Gibbons was a marvelous, energetic communicator and an intense competitor. For example, early in 1972, he was invited to the International Symposium on Streptococci and Streptococcal Diseases at the University of Minnesota (forerunner of the Lancefield Symposium...Rebecca Lancefield, the grand-aunt of all researchers who study streptococci, was in the audience!). Ron was scheduled last in the day to speak about indigenous oral streptococci, certainly not a saliva-stimulating topic for a crowd longing for dinner and used to debating acute epidemics, rheumatic fever, glomerulonephritis, and what we now call flesh-eating disease. Ron mesmerized them with the oral ecology-adhesion story, and then dared to dangle some data, obtained by post-graduate student Richard Ellen, which implied that pathogenic *Streptococcus pyogenes* followed the same principles of adhesion-dependent colonization of cells in the upper respiratory tract. This was the first public broadcast of Ron's adhesion hypothesis to medical microbiologists outside dentistry, and of course they did not believe him. Yet following its publication, some of the meeting participants could not help being drawn into the field, including Edwin Beachey, who became an outstanding leader in adhesion of *S. pyogenes* and *Escherichia coli.*

That was "infection". Ron next tackled "immunity". The paper that probably catapulted his Forsyth team to recognition outside dental research was Ray Williams' and Gibbons' 1972 publication in *Science* that identified prevention of specific bacterial adhesion as the major function of secretory IgA. Think of the impact this must have had on contemporary concepts of ecology, pathogenesis, and immunization strategies for all sorts of parasites that infect the host's diverse mucosal surfaces! The duo followed with a publication ascribing adhesion-inhibiting functions to other classes of salivary glycoproteins. Over a period of five short years, Gibbons and company literally opened entirely new research doors and careers for many others in medical microbiology and acquired and innate immunity. Ron went on to lead the bacterial adhesion field for 20 more years and made many more novel contributions relating to bacterial adhesion mechanisms (Table 1), with trainees like Bill Clark, who developed the field's standard assay for bacterial adhesion to saliva-coated hydroxyapatite, and close collaborators Ed Moreno and Don Hay. Interested *JDR* readers can learn more details about these and subsequent adventures in bacterial adhesion directly from the source by reading a *Discovery!* article written by Ron Gibbons shortly before his untimely death (Gibbons, 1996).

Table 2. The Legacy of a Mentor—Ron Gibbons' Trainees with Full-time Academic/Research Careers*

Trainee	Country
Walter Loesche	USA
Wilson De Araujo	Brazil
Ilka Paunio	Finland
Johannes van Houte	The Netherlands ➔ USA
Jan Doekes De Stoppelaar	The Netherlands
Tabara DaCosta	Brazil
Jens Kelstrup	Denmark
Jeffrey Hillman	USA
William Liljemark	USA
Richard Ellen	USA ➔ Canada
Ray Williams	USA
Jaime Bulkacz	Argentina ➔ USA
Douglas Bratthall	Sweden
Page Caufield	USA
William Clark	USA
Howard Howell	USA
Lili Luschke Bammann	Brazil
Jørgen Slots	Denmark ➔ USA
Bruce Paster	USA
William Peros	USA
Yuko Naito	Japan
Tianjia Liu	China

* Trainees include undergraduate, graduate, and post-doctoral research trainees, as well as dental interns at the Forsyth Dental Center, who engaged in research and were influenced to pursue academics as a full-time career. Ron Gibbons also had several trainees who went on to distinguished careers in the health professions, and he was a strong role model for numerous young investigators who started their research careers during his years as Associate Director for Research and then Director of the Forsyth Dental Center.

HOW RON GIBBONS WAS PERCEIVED INTERNATIONALLY

Ron Gibbons' leadership in research was both recognized and admired internationally for its conceptual novelty, insight, and quality. His laboratory became a magnet for colleagues from the world over to pursue post-doctoral training or merely to discuss new science and to get inspiration. When we asked Bo Krasse, the "grand-professor" of Scandinavian cariology, who was attracted to the Forsyth Dental Center for a sabbatical year, his immediate opinion of Ron was, "a really original thinker, so open in his attitudes and always willing to take time for constructive discussions". For example, Krasse had once noted that Ron so willingly revealed his most recent laboratory results in discussions with foreign visitors. Ron answered that if someone else could take such "insider information" and do the research better or faster, then s/he should do it...both generous and confident. Ron rarely got "scooped"!

Another aspect much appreciated by the international community was Ron's ability to present his new research results in context, not just a summary of data, tables, and figures. He was a "big picture" communicator, a forerunner of what we call "knowledge translation" today. He formulated his

messages to fit global concepts, readily comprehensible to international audiences and compatible with international perceptions. During "the Gibbons years", it was customary for many colleagues around the world to dive into the annual IADR abstracts book upon its arrival to search for Gibbons' papers. Needless to say, he always drew a crowd. An illustration of international respect and appreciation for his impact was the granting of honorary doctorates at Göteborg University, Sweden (1977), and Utrecht University, The Netherlands (1981). Ron was under 50 years of age at the time.

Those of us who worked with him, from so many backgrounds and countries, fondly remember the daily routines of this incredibly productive investigator: the early morning coffee and small talk; the daily check of lab results; his encouraging phrase for marginal data, "the results are trying to work"; the informal atmosphere; the cluttered small desk full of papers; the pull-out writing tablet, where so many seminal articles were drafted on pads of lined yellow paper (a practice Ron picked up from Macdonald); his intense concentration; and always so absorbed in his thoughts. He was an investigator of enormous merit and not a politician; yet he served as the sixth President of the AADR in 1977-78. A great scientist and an unparalleled mentor was Ron Gibbons, whose list of trainees (Table 2) is proof enough of a legacy of international scope and lasting impact.

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