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The tooth as a model in organogenesis

An interview with Professor Harold C. Slavkin

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Organogenesis is a complex process in which, as a result of several instructive and permissive cell-cell interactions, there appear new cell strains, precise modifications of the extracellular matrix, morphological and topographical changes and new tissue functions. This set of alterations occurs within a specific sequence in which regional alterations take place one after another until, finally, well defined organs emerge wholly integrated into the general physiology of the organism they are part of.

The secondary induction mechanism within developing organs is usually analyzed through the study of experimental models from which general hypotheses applicable to most tissue complexes may be inferred. Tooth is undoubtedly one of the most complete, and most useful, of such models. The ease with which it lends itself to experimental study, to *in vitro* cultivation and cytological and molecular analysis, together with the precise delimitation of its presumptive territories (dental papilla and dental lamina), the morphological characteristics of its typical cells (odontoblasts and adamantoblasts), the spectacular changes in its extracellular matrix and subsequent secretion of products (predentine/dentine and enamel), and its patterns of mineralization and regional differences (e.g. between incisors, molars, etc.) – all these things make tooth a unique model with extraordinary appeal for developmental biologists and obvious medical significance.

For decades now, a number of outstanding scientists have explored the advantages of tooth as a model for the experimental study of organogenesis by applying a wide range and variety of techniques, mainly in the fields of cell and molecular biology. Since among these investigators one of the most distinguished over the past twenty-five years has been Professor Harold Slavkin, we felt that a good way of introducing the subject would be to review the enormous scientific progress achieved in this field through an analysis of his highly enlightening career.

Harold Slavkin was born in 1938 in Chicago, Illinois, the first son of a Russian couple who in the previous decade had emigrated from the Soviet Union. His parents — his father was a pharmacist, his mother a nurse — were very young when they arrived in the United States with their respective families and adapted to their new homeland with all the enthusiasm and tenacity of pioneers. At the same time they managed to imbue their own children with what they saw as the new, specifically American values, while also providing them with a European cultural background. This mixture of Old and New World qualities made a profound impression on the young Harold Slavkin: "my parents shared beliefs that anything was possible and that the art of criticism was a valuable part of living; they loved family, friends, card playing, Mozart, Chopin, Beethoven and Picasso, Monet and books; they modeled for their children traditional first-generation American values: work hard ... be the best you can ... life is fair ... always be kind to others." The quality of perseverance and the constant need to do better inculcated in him during his childhood and youth were to become a hallmark of his professional career, and they have also contributed to making Harold Slavkin the attractive and somewhat unusual figure he is today.

Shortly after the Korean War, at the tender age of 17, Slavkin joined the US Army Dental Corps as a technician and began work at the Walter Reed Army Medical Center's huge dental laboratory in Washington D.C., where he remained for three years. The money saved during his army service was put towards a University education, and he graduated from the University of Southern California in 1961. He was then hired as Research Technical Assistant by the Department of Anatomy of the University of California's School of Dentistry and Medicine at Los Angeles and, once again, Slavkin put the money earned there to good use: his savings funded his studies in dentistry and he was awarded his

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DDS in 1965 from the University of Southern California. Postdoctorate work now followed, under the guidance first of Professor Richard Greulich at UCLA's Department of Anatomy and later, at the USC Biochemistry Department, under Professor Lucien Bavetta, who was to be a decisive influence in Harold Slavkin's personal and professional development. However, one of the major problems of this in part self-financed education was the accumulation of considerable debts, and Slavkin worked as a private dentist while still engaged on his postdoctoral research. All this activity did not prevent him from publishing his first research paper on the process of odontogenesis, which appeared in *Nature* (vol. 127, pp. 269-270) in 1968. During those years, a growing interest in developmental biology, immunogenetics and the new discipline of molecular biology led him to attend the Gordon Conferences in New Hampshire, the Marine Biological Laboratory at Woods Hole and the Philadelphia-based Hahnemann Conference on Epithelial-Mesenchymal Interactions which, in his own words, shaped the rest of his professional life.

A five-year Research Career Developmental Award from the National Institutes of Health provided the support he needed to establish himself as an independent scientist. At first, he aimed to cover a number of topics related to odontogenesis, including studies on the dissociation, recombination and reconstitution of tooth germs designed to discover the cellular interactions established between components during embryo development, electronic microscopy analyses of cell-cell contacts between epithelium and mesenchyme, and research on the specific inductive properties within the extracellular matrix of developing mammalian tooth organs.

The latter field was to have particular importance for Slavkin, and was to take up much of his research energies over the following years. In 1972 and 1974 he helped to organize two successive Conferences, on California's Santa Catalina Island, on the extracellular matrix influences on gene expression. These conferences foreshadowed some important discoveries in developmental biology such as the role of growth and transcription factors. After publication, the Conference papers were to be much quoted in other works of the time published the world over and also helped Professor Slavkin's group to set up new international research collaborations of which they are especially proud, and which they have fostered ever since. In 1974, Slavkin published an important monograph entitled *Tooth Formation: A Tool in Developmental Biology* covering both his own research and the current state of odontogenesis studies and which was soon recognized as a classic on the subject.

Around this time, the second phase of Dr. Slavkin's scientific career started, when he began to concentrate on the molecular biology of tooth development. One of the major reasons for this particular direction was his time at the NIH's National Institute for Dental Research at Bethesda, Maryland, where his previous mentor Richard Greulich was Scientific Director of the Intramural Research Program. At Bethesda, he had the opportunity of working with and learning from scientists like George Martin, Vince Hascall and Robert Pratt. From the late seventies to the present, Slavkin's personal research and that of his large group of co-workers has been oriented along two basic lines. The first of these lines is the molecular biology of enamel, dentine and cementum, in which the isolation, characterization and cloning of the mouse amelogenin, the major protein component of the extracellular matrix of developing dental enamel, was particularly interesting and important. The other fundamental line pursued is the role of the growth factors, their receptors and some transcription factors in tooth and mandibular development.

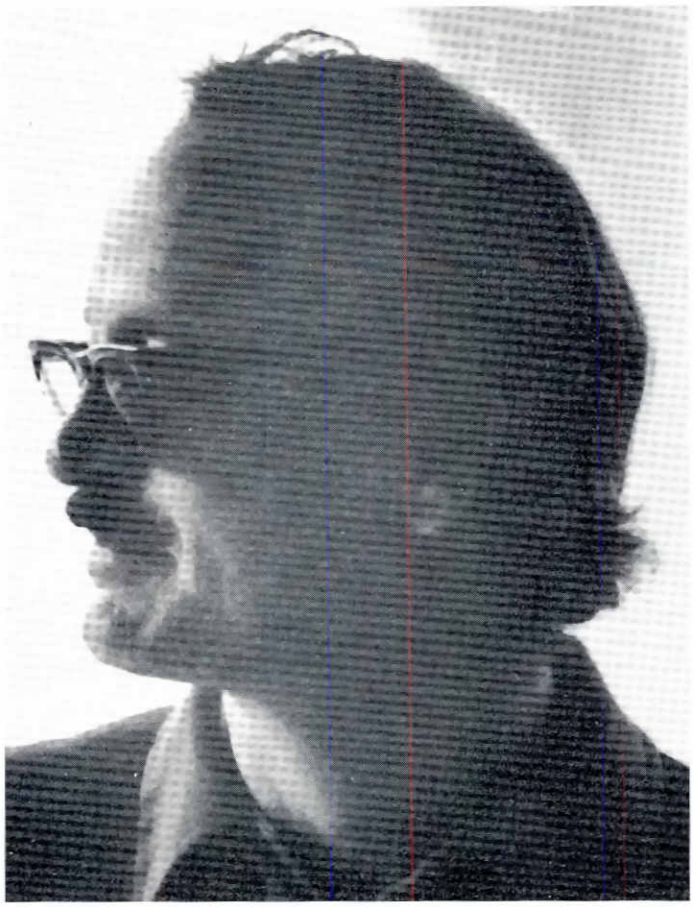
Other major research that should also be mentioned includes work done on the search for a serumless chemically-defined medium that would permit *in vitro* tooth development, development studies and genetic and teratological approaches to craniofacial development. However, perhaps Professor Slavkin's most outstanding personal feature is his flair for organizing and motivating everyone around him. This flair is reflected in his record at the University of Southern California — as Chairman of Biochemistry (1969-1975), Director of the Graduate Program in Craniofacial Biology (1974-1985), Chief of the Laboratory For Developmental Biology (1973-1989) and Director of the Center For Craniofacial Molecular Biology (1989-present) — a record which, taken as a whole, is undoubtedly his finest professional achievement and one of which he can be justly proud.

We hope the following interview gives a more personal view of our subject, and reveals a little more about his true standing as an original, dynamic and outstanding scientist researching in the field of dental and craniofacial development.

At first glance, your dental vocation would appear to be the result of your time at the Walter Reed Army Medical Center. Are you aware of any other motivation from childhood, say, or your youth, particularly bearing in mind your parents' professions?

Like many other developing young people, I was drawn to a number of intellectual and creative areas including art (watercolor), sports (basketball and baseball), English literature, the Humanities and Science. My parents always encouraged me to consider a career in the health sciences. In secondary school, I felt I would like to become an artist. After graduation, with some troubling adolescent circumstances, I joined the US Army at the age of seventeen for three years, and was trained to be a dental technician by Dr. Henry Sutro (a drafted San Francisco dentist with superb restorative dentistry talents) at Fort Sam Houston in San Antonio, Texas. I was then stationed at Walter Reed Hospital in Washington, D.C. While in Washington, I began my university education by attending the University of Maryland Extension at the Pentagon in the evenings and identified "English literature" and "dentistry" as my career goals. Washington also offered me opportunities to explore science, art, history, museums and politics. It also became evident that I would seek a so-called "classical education in the humanities" before attending a professional school. This decision was prompted in no small measure by a remarkable friend and mentor named Max Ferber. My plans were realized as I became a USC undergraduate in 1958 majoring in English literature and biological sciences supported by an academic scholarship. My undergraduate education was enriched by many people including my classmates Bob Shuken (currently a maxillofacial surgeon), Peter Rosen (now a medical oncologist at UCLA) and Dick Appel (now an architect). In 1961, married and with one child, I entered the USC School of Dentistry and graduated in 1965. Of course, I remain unconditionally appreciative of my parents' human values and I am supportive of the humanities, reading fine fiction and non-fiction, and the pursuit of a life-long love for watercolors.

In the sixties, it must have been exceptional for a student of dentistry like you to take such an interest in basic research. What were the specific reasons behind such an unusual decision?

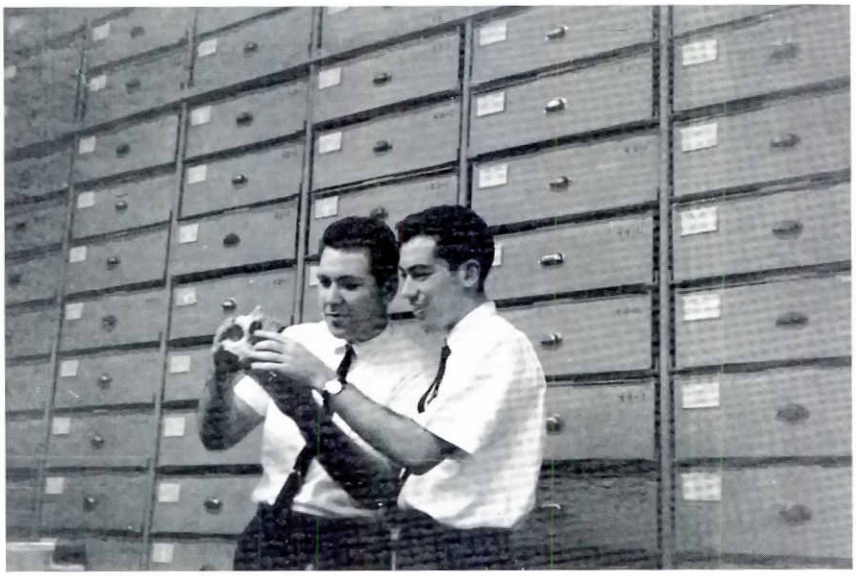


Dick Greulich and Lucien Bavetta (1907-1982), outstanding scientists and scholars. Both were mentors of Harold Slavkin's.

Yes! In the early 1960s at the USC School of Dentistry it was a "novelty" for dental students to seek opportunities in research. I suspect that a few of us actually began a "trend" at USC; perhaps this was a similar situation at many other schools of dentistry or dental medicine. Succinctly, the major "force" in my scientific odyssey were the human beings who inspired as well as challenged my intellectual interests. As a freshman dental student I became impressed with the intelligence and spirit of Professor Lucien Bavetta who taught biochemistry and nutrition. Bavetta was an inspiration! In my second year (1962), I joined with two other dental students, Stan and Marvin Cantor, and we forged a research project and team to investigate the possibility of a new clinical approach to the second division block of the trigeminal ganglia via the pterygopalatine canal and fossa. Our anatomy professor, Bob Greg, was supportive. We obtained a modest travel grant from the USC School of Dentistry which enabled the three of us to have the experience to carefully measure numerous anatomical relationships using the child and adult skull collections at Case Western Reserve University in Cleveland, and the Smithsonian and Howard University Collections in Washington, D.C. We made this journey over our two-week Christmas Vacation in 1962. The process of inquiry, cooperative learning with peers and the analyses of the data was enormously inspiring. The eventual publication of our efforts was very satisfying. It was enormous fun to learn with Marv and Stan Cantor! The following year, I was serving the oral health needs of a dental patient in the USC Clinic who presented an "amputation neuroma." It was fascinating to make the diagnosis and to then learn how rare this disorder turned out to be. This encouraged me to learn with Professor Marsh Robinson about amputation neuromas and we wrote a brief review and presented this new case report into the literature. In 1964, I met Professor Richard Greulich at the IADR Meetings which were held in Los Angeles. He offered me a part-time research position in his lab at UCLA during my senior year of dental school at USC. It was exciting learning about autoradiography and special histochemical procedures and their application to dental extracellular matrix formations. Dick Greulich was critical for my journey into research!

Your postdoctoral training was a particularly important phase of your career. Could you tell us something about that time and, specifically, about the impact of professors Richard Greulich and Lucien Bavetta on your subsequent work and development as a researcher?

During my senior year of dental school at USC I began to study with Professor Richard Greulich at UCLA, then the Chairman of the Department of Oral Biology in the UCLA School of Dentistry scheduled to open in the next few years. After I graduated from USC School of Dentistry in June, 1965, I joined Dick as a postdoc and continued our shared interests in protein biosynthesis and secretion during tooth development using autoradiography. Dick Greulich was a fantastic mentor. He modeled the very best of



Hal Slavkin (left) and Stan Cantor (right) investigating the pterygopalatine canal and fossa at Howard University in December, 1962 *(see Slavkin, H.C., Cantor, M.R. and Cantor, S.R., 1966. An anatomic study of the pterygomaxillary region in the craniums of infants and children. Oral Surg. Oral Med. Oral Pathol. 21: 225-235).*

scholarship and integrity. His seminars, lectures and writings were always superb! I was determined to learn these skills. During that very productive phase in my career (1965-1966), Dick was recruited and accepted a position at the NIDR in Bethesda, Maryland. He invited me to join him but I decided to stay in Los Angeles, to continue my part-time dental practice (i.e. Tuesday and Thursday evenings and all-day Saturdays) to support by wife and two children, and to continue postdoctoral training at USC with Professor Lucien Bavetta. Lou was another remarkable mentor. He was child-like, curious about everything and keen to nurture my scientific odyssey. Whereas his expertise was in the biochemistry of collagen, specifically inter- and intramolecular crosslinking, he was unconditionally supportive of my interests in developmental biology. He supported my taking classes in advanced biochemistry with special emphasis upon nucleic acid chemistry. He enthusiastically supported my attendance at a course at Woods Hole in embryology, at several Gordon Conferences, and trips to visit the laboratories of Professor Clifford Grobstein (then at UC-San Diego), Professor Norman Wessells (at Stanford) and Professor Aaron Moscona at the University of Chicago. Lou sponsored me for a Research Career Development Award (RCDA) from the NIDR and this became a superb venue for a career in biomedical research (1968-1972). For me, Lou's legacy was his passionate dedication to fairness, kindness and a love of "what people could be." I have spent my entire adult life trying to reach the standards modeled by Lou Bavetta — he was one of a kind!

How would you describe the scientific atmosphere in Developmental Biology in the late sixties, particularly regarding organogenesis?

Developmental biology in the 1960s was very exciting and has remained a wonderful pursuit ever since. In the 1960s we marveled at the discovery of the genetic code and the realization of ribosomal, transfer and messenger RNAs. Gordon Conferences were organized to focus on cell-cell communication, epithelial-mesenchymal interactions and the emerging nucleic acids and protein markers for development in numerous invertebrate and vertebrate systems. The 1960s were dynamic! Grobstein's transfilter studies, Bea Garber's tissue dissociation and reaggregation experiments, Bill Rutter's critical analyses of pancreatic development and his discovery of a sequence of protein expression which characterizes the phenotype, Jerry Gross' postulate for the morphogenetic role of collagen in development, Norman Wessells "rules" for organogenesis and inductive tissue interactions and the many, many other discoveries which resounded in the 1960s. At the same time, the field was small enough for most participants to become acquainted with one another, to have sufficient support for research and this fostered numerous collaborations and life-long friendships.

What were your first attempts to make tooth into a reliable model for the *in vitro* study of cell interactions during embryo development?

After numerous discussions with Edwin Cooper (developmental immunology) and Fred Herzberg (zoology and the resistance of garden snails to irradiation) at UCLA and later with Lucien Bavetta (collagen biochemistry) at USC, I decided to replicate and extend the earlier efforts of Shirely Gladstone in culturing embryonic or fetal mammalian tooth organs on the chick chorio-allantoic membrane (CAM). My simple experiments provided a revised model for studies of rodent tooth organogenesis in an artificial system from early cap stage to the completion of crown development. While flying from Los Angeles to San Diego in a small plane, I observed from the air the highly ordered assembly and disassembly of US Marine recruits at Camp Pendelton. How do they know when and where to assemble or disassemble? What is the signal and how is it received and processed? These questions led me (and others) to design experiments which dissociated the cervical loop tissues of continuously growing rodent or rabbit incisor teeth and to analyze when and where these heterologous dissociated cells reassembled. One curious observation was the formation of a metachromatic basement membrane in those areas where heterologous cells reassembled into tissues that were complementary to the odontogenic phenotype. How do cells recognize self and non-self and how do these cells assemble into sheets (epithelium) and produce a basement membrane in juxtaposition to the dental papilla ectomesenchyme? Do odontogenic cells reassemble by rules similar to those followed by sponge cells? Further, do these heterologous tissues "signal" one another and what is the chemical basis for intercellular communication? If heterotypic cells communicate through an extracellular microenvironment, could one isolate a "message" from the matrix? I read the work of Paul Weiss of the Rockefeller University. My early efforts led to questions which then led to additional questions. I have been engaged in asking such questions for nearly 30 years! Ironically, the questions appear to remain the same but the answers change as we learn about the molecular nature of morphogenesis. I read Aristotle's "Principles of Biology" and discovered that he in fact raised some of these questions 2,000 years ago.

This brings us to the methods for organotypic culture of tooth germs. In your opinion, what are the basic nutritional requirements in serumless chemically-defined medium, and what do you feel you have contributed personally to this field?

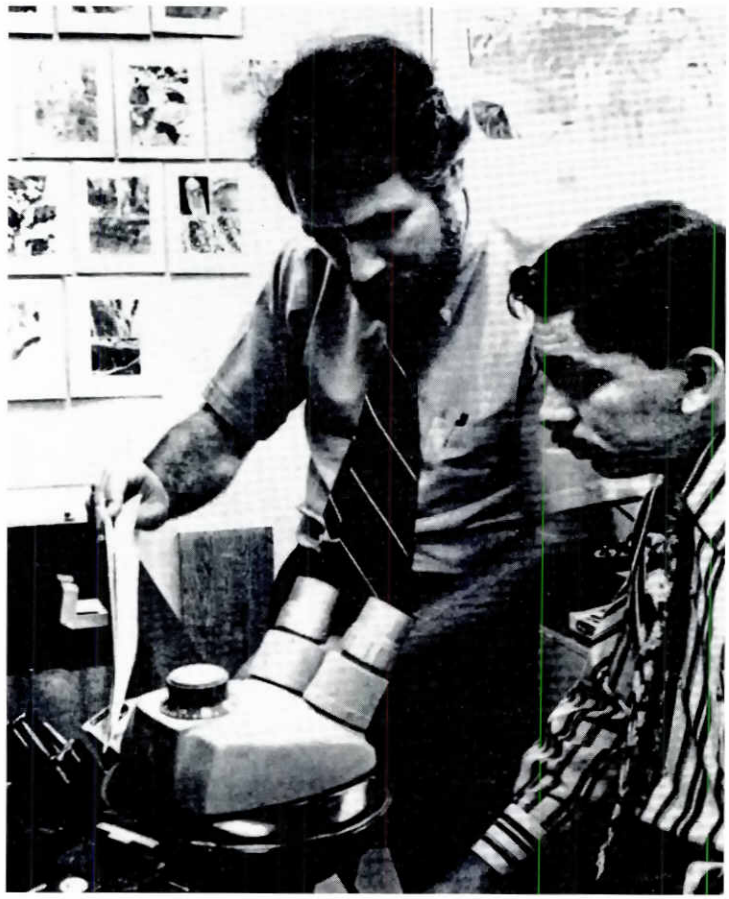
After these many years of exploring how to identify environments suitable to support inductive and permissive heterotypic tissue-tissue interactions, we have learned that simple medium (e.g. buffered pH conditions and essential nutrients) are permissive for complex processes when one initiates the *in vitro* culture during mid-gestation (e.g. in mouse embryogenesis at 10-11 days gestation). Mandibular processes, palatine processes, ear rudiments, lung rudiments, limb buds and early cap stage molar tooth organs as explants all express remarkably complex histological and molecular phenotypes using serumless medium. For example, E10 lung explants express branching morphogenesis, produce lamellar bodies and express and secrete pulmonary surfactant in serumless medium. E14/15 mouse molar tooth explants express multiple cusps, dentine and enamel tissue-specific biomineralization and even root formation in serumless medium. We assume that endogenous growth factors (e.g. including vitamin-like molecules) provide the essential cues required for complex development in these artificial environments.

Hal Slavkin with Cliff and Ruth Grobstein (UC-San Diego) at the Second International Santa Catalina Island Conference "Extracellular Matrix Influences On Gene Expression" (1974).

Extracellular matrix biology has concerned you closely over the last twenty-five years. As a scientist who's been very much involved in this field, how have the concepts governing this area of research changed, with regard to embryonic induction processes? What prospects do you see for the future here?

Extracellular matrix biology evolved from a number of disparate types of investigations which attempted to understand significant biological processes that appear to be initiated and regulated within the extracellular microenvironment. Progress in this area was driven by international conferences designed to optimize communication between scientists from very different fields of inquiry and by advances in technology such as immunocytochemistry, western transfer methods and a number of micromethods in cellular, developmental and molecular biology. For example, how do procaryotic or eucaryotic cells regulate extracellular biomineralization? Studies designed to understand the initiation and propagation of cell- or tissue-specific biomineralization were pioneered by the inspiring efforts of the late Professor Heinz Lowenstam from the California Institute of Technology in Pasadena. Heinz and Steve Weiner, in particular, mobilized scientists (myself included) from the physical, earth and biological sciences to focus on this problem area.

In a different context, how do heterotypic tissues communicate during induction? Cliff Grobstein and Lauri Saxén elegantly showed the transfer of bioactivity from tissue to tissue vis-à-vis an interposing Millipore or Nuclepore filter. Heterotypic tissues communicated either by direct cell-cell contact, through short-range diffusion of morphogenetic molecules (e.g. growth factors binding to their cognate receptors), or by cells secreting morphogenetic molecules into a forming extracellular matrix (ECM), which in turn induce adjacent cells to express a specific phenotype. It was in such an intellectual environment (1967-1974) that I initiated investigations of the interface or basement membrane interposed between epithelium and mesenchyme during tooth development. At that time a graduate student, Richard Croissant assumed that inductive molecules were transferred between heterotypic tissues during inductive epithelial-mesenchymal interactions. What were these molecules and how did they infer specificity? It seemed logical to assume that the biologically active inductive molecules could be isolated and characterized from extracts of the extracellular matrix interposed between interacting heterotypic tissues. The developing rabbit or rodent incisor tooth organ at the cap and early bell stages seemed an ideal model for such inquiries. At that time Richard Croissant and Pablo Bringas isolated the extracellular matrix (ECM) and began a process to characterize the bioactivity of the ECM (1967-1970) and to isolate and characterize putative morphogenetic matrix vesicles containing RNAs (the completed PhD studies of Richard Croissant, 1970-1974). Thereafter, our orientation evolved to seek morphogenetic molecules derived from the dental papilla ectomesenchyme that would induce *de novo* enamel expression from the adjacent enamel organ epithelium. As several papers within this special volume elegantly demonstrate, we now realize that an odontogenic ectodermal placode signals adjacent cranial neural crest to aggregate into progenitor odontogenic ectomesenchyme and thereafter dental papilla mesenchyme regulates the size and shape of the resulting tooth organ. Further, we now realize that a number of different growth factors bind to their cognate receptors through autocrine and/or



Hal Slavkin and Pablo Bringas became colleagues and close friends and have been working and learning together since 1968 *(photo circa 1977).*

paracrine processes and control the sequence and duration of the stages of tooth morphogenesis. Further, we now appreciate that null mutations of selected growth factors, cognate receptors and transcription factors in transgenic animals produce newborn pups with adontia or hypodontia. The future is bright with numerous opportunities for studies to advance a molecular and structural biology of tooth morphogenesis.

Another interesting feature concerning tooth differentiation is your research group's search for specific molecular markers. What personal influence did your time at the NIDR at Bethesda in the mid-seventies have on this work, and what do you feel have been your most important contributions since then?

Another turning point in my career was the opportunity to learn with very bright scientists at the NIDR in 1975. At that time Karl Piez, Ted Miller, Paul Bornstein, Bill Butler and George Martin were world leaders in connective tissue research. John Termine was advancing the biophysics of ECM biomineralization, George Martin and Hynda Kleinman were pioneering the chemistry and immunology of ECM molecules, and George Martin and a number of his postdocs including Maggie Zeichner-David were developing the use of cell-free translation techniques to characterize alpha type 1 collagen mRNA. George invited me to serve as his substitute (there can be no substitute for George Martin) as Acting Lab Chief of the Laboratory For Developmental Biology and Anomalies at the NIDR while he went to the Max Planc Institute in Munich to learn immunology applied to collagen molecules. The NIH environment was fantastic! Each hour of each day there were world-class seminars and workshops. I quickly seized this unique opportunity and realized that cell-free translation and other molecular methods could be applied to developing tooth organs; specifically, nucleic acid chemistry and immunochemistry to characterize the gene products of the rabbit and sheep enamel organ epithelium. In collaboration with Maggie Zeichner-David, we developed a system for subsequent characterizations of enamel gene products. In fact, I recruited Maggie to join us at USC in 1977 and she has been with us ever since. The NIH intellectual environment with people advancing molecular approaches to biological problems transfected my thinking and I became irreversibly transformed into an advocate for molecular approaches in developmental biology.

Since the late seventies, your laboratory has made some major contributions to the field of the molecular biology of cementum, dentine and enamel, as well as to the role of growth factors in odontogenesis. Could you give us a general summary of your results?

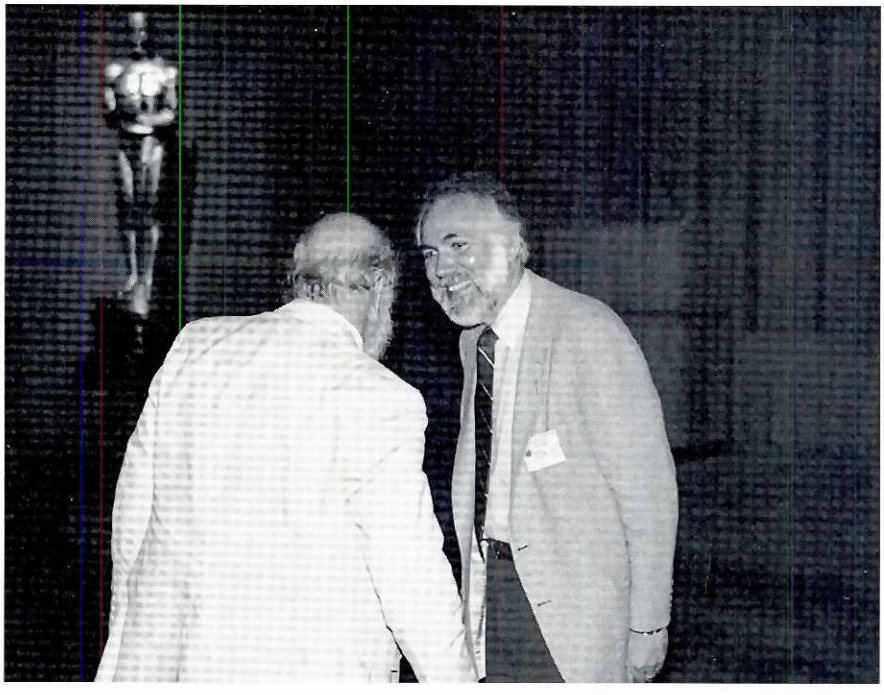
After my brief experience at the NIH, I was convinced that future progress in tooth development would require pioneering efforts in the characterization of unique molecules which might characterize the enamel, dentine and cementum phenotypes. In 1980, my wife Lois and I met Savio Woo (Baylor University in Houston) at the San Francisco Airport where we discovered that we were going to travel together to attend a unique international conference "The Role of RNA in Development and Reproduction" organized by Professor M.C. Niu in Beijing, China (April 25-30, 1980). At this conference I was especially privileged to meet a number of outstanding American scientists including Vincent Allfrey, French Anderson, David Baltimore, Jim Darnell, Marv Fishman, Walter Gilbert, Bob Goldberger, Paul Gross, Larry Kedes, Severo Ochoa, Bob Roeder and M.A.Q Siddiqui and a very large number of Chinese scientists. Savio and I talked for hours and days about the new possibilities to characterize the genes involved with enamel production. At this time, my colleague Maggie Zeichner-David had clearly shown multiple enamel transcripts using cell-free translation. We formed a terrific collaboration which subsequently evolved into our sponsoring a young postdoc named Mal Snead to spend six months in Houston in Savio's lab to produce a cDNA for mouse amelogenin. Thereafter, with the extraordinary good fortune of learning and working with outstanding colleagues in our laboratory (e.g. Maggie Zeichner-David, Mal Snead, Alan Fincham, Mary MacDougall, Ed Lau and more recently Jim Simmer and Janet Oldak) we made a number of seminal discoveries related to the enamel, dentine and cementum gene products. For example, we were the first group to produce a polyclonal antibody to amelogenin, to produce a cDNA for amelogenin, to map amelogenin to the mouse X chromosome, to map amelogenin to the human X and Y chromosome, to indicate the association between the amelogenin gene and X-linked amelogenesis imperfecta (AI) and to characterize the multiple amelogenin transcripts produced by alternative splicing in the mouse model. In tandem, our group was the first to characterize precisely when and where amelogenin and enamelin (e.g. "tuftelin")

transcription takes place during mouse tooth development; tuftelin at E13 (bud stage) and amelogenin at E15 (cap stage) well in advance of the secretion of enamel proteins associated with extracellular matrix biomineralization.

Your interest in the developmental biology of the tooth has extended to the study of congenital craniofacial malformations. Could you tell us a little about your studies in experimental teratology and of its clinical and scientific importance?

This is an interesting question. As a dental student I was intrigued by congenital craniofacial-oral-dental dysmorphogenesis. When, where and how are these deformities created during the embryonic or fetal stages of human development? In 1968 I met Sam Pruzansky (University of Illinois in Chicago) who coined the term "craniofacial biology." In 1972 Sam and I wrote a position paper for the NIH on craniofacial malformations and we both worked as advocates for this field of study, essentially making the argument for increased federal funding for basic and applied research in craniofacial malformations. Also, in 1970 I met Ray Owens at Cal Tech and learned about his fascinating immunogenetic studies. Ray observed that specific strains of mice were more or less susceptible to tumor formations. About that time, Joe Bonner approached me and asked if I would serve as his mentor for a PhD in Cell Biology at USC. Joe was keen to investigate a problem using the powerful tools of immunogenetics. So we designed a study to test the hypothesis that genes within the Major Histocompatibility Complex (MHC) regulate steroid-induced cleft lip and palate in highly inbred strains of mice. Using congenic mouse strains (H-2^a versus H-2^b), blastocyst transfer and statistical techniques we were able to show for the first time that the MHC contains genes that control relative resistance or susceptibility to drug-induced cleft lip and palate. This work was originally published in IMMUNOGENETICS in 1975. We then extended this work with Paul Terasaki at UCLA to examine a possible association between human HLA phenotypes and cleft lip and palate frequencies. These studies introduced me to a number of very talented maxillofacial plastic surgeons such as Libby Wilson (Rancho Los Amigos, Downey, California) and Hank Kawamoto (UCLA) who were strong advocates for learning more about the biology of craniofacial dysmorphogenesis. At that time I recruited Mike Melnick to join our lab; Mike was trained at the University of Indiana by Professor David Bixler as a DDS/PhD with specific interest in craniofacial disorders. After Mike completed a postdoc at the NIH he joined me at USC. Our shared interests revolved around the inter-relationships between genetics and developmental biology, and the mouse MHC model served as an excellent example of these relationships. In addition to a number of studies that we performed together, in 1979 Mike and I started the *Journal of Craniofacial Genetics and Developmental Biology* and we have co-edited the journal since 1980.

I have been directly engaged in thinking about craniofacial-oral-dental dysmorphogenesis since 1968 and my fascination with this areas has never diminished in all of these years. Our most recent efforts have been towards understanding how mutations in morphoregulatory molecules such as growth factors and their cognate receptors result in human congenital craniofacial malformations. For example, mutations in EGF and Rieger syndrome or mutations in FGFR and Crouzon syndrome.



Jean-Paul Revel and Hal Slavkin enjoying the film "A Lifetime of Change" produced for the ISDB Congress in Los Angeles and shown at the Academy of Motion Pictures, Arts and Sciences in Beverly Hills in 1985.

One of the more surprising features of your scientific career is the interest in comparative morphology. What prospects do evolutive studies offer for a better understanding of craniofacial and tooth embryological research?

I have always been intrigued with the intellectual synthesis between evolutionary and development biology. Early on it became evident that developmental processes observed within the developing rabbit, rodent or human dentition began significantly earlier in evolution. Therefore, I have attempted to learn and reflect upon the genesis of tooth morphogenesis from hagfish to philosopher. What is frustrating, however, is that access to an extant species (assumed to represent a specific position on a cladogram) does not necessarily represent the comparable creature that lived 500 million years ago as in the case of early chordates — hagfish and lampreys. Undaunted, we have pursued these issues for several decades through the wonderful and catalytic discussions with the late Bill Hildemann at UCLA, Stephen Jay Gould at Harvard and Dick Krejsa at Cal State-San Luis Obispo, California. When in evolution do tuftelin and/or amelogenin genes first appear? What determined the transition from enameloid to enamel? What regulates the formation of the dentine-enamel junction in selected vertebrates? How do transcription factors (e.g. Msx-1. Msx-2, Dlx-2, LEF-1 and others) interact in various combinations to

The remarkable human resources of the Center For Craniofacial Molecular Biology as of the summer, 1992. CCMB was envisioned and designed in 1989 and "lived in" since February, 1990.

control the patterns of tooth morphogenesis which characterizes a specific organism? I believe that the recent discovery of the homeotic gene code in early prechordates is very exciting and offers numerous research opportunities towards understanding the "rules" for tooth initiation, size and shape. I see the future as being very exciting in this area.

The Center for Craniofacial Molecular Biology is the happy result of an idea nurtured by you over many years. Could you give a brief account for our readers of the Center's origins, its current organization, how it works and its future as you see it?

The Center For Craniofacial Molecular Biology (CCMB) was envisioned in 1989 as an environment which would encourage and sustain fundamental research into the problems of human development in general and craniofacial-oral-dental genetics and development in particular. I was presented with a unique opportunity by the Dean of the School of Dentistry (at the time Bill Crawford) and the Senior Vice President For the Health Sciences (Joe Van Der Muellen) to create a Center of approximately 15,000 square feet on the Health Sciences Campus of USC in 1989. We were very fortunate to recruit a remarkable architect, Kenneth Kornberg (son of Arthur Kornberg at Stanford who discovered DNA polymerase) for this project. Ken has designed a number of world-class environments for research and we were fortunate to have his excellent services. Our CCMB faculty all worked together and forged a vision that Ken translated into structures and design elements. We moved into the new Center space in February, 1990. Our working philosophy was to create optimal space for maximal human-human interactions, to nurture training, to foster communication and shared resources and an environment that fosters the joy of discovery. Five years later we feel that structure supports the functions — a fine example of morphogenesis.

More specifically, we are 12 full-time faculty with postdocs, graduate students, college and high school students, research technicians and an administrative support team totaling 72 people. Our mission is research, training and out-reach to the professional and public communities. Our organization is faculty-centered and the faculty serve as an executive council for the Center Director. Our faculty have joint-appointments with other units in the University including the Graduate Programs in Craniofacial Biology or Molecular Biology, the Norris Cancer Center, the Institute for Genetic Medicine and the Departments of Pediatric Medicine, Otolaryngology, Plastic Surgery and Oncology. Several of our faculty serve as Directors for Graduate Programs. Several of our

faculty are engaged in research projects both within this university and at a distance (e.g. Japan, France, The Netherlands, Great Britain and Israel. Our funding is essentially derived from three sources: (1) competitive NIH and NSF research and training grants, (2) the School of Dentistry, and (3) private individuals, foundations or corporations. In 1995 our total budget is approximately five million dollars.

The future would seem very bright! Our parent School of Dentistry under the leadership of Dean Howard Landesman and our University are dedicated to research and training. The opportunities for creativity are without limit! As an "administrator" my challenge is to obtain and sustain the resources required to enable the pursuit of creative research and to nurture the next generation of future scientists.

Throughout your professional career, you have devoted a great deal of your time and energies to organizing scientific encounters. You have also visited many research centers all over the world. How important do you think international contacts and relations are to the development of science?

I sincerely believe that science is a "verb" (doing science) and a way of knowing. In this context, human creativity and human interactions provide the engine for originality and accomplishment. For me, the people of science have been and continue to be the best part of doing science and the international nature of science must always be nurtured. There are too many individuals to cite in any detail but a few international opportunities seem particularly important in my scientific odyssey. I will never forget Alan Boyde in London teaching me about his discoveries with SEM and a sailing adventure in 1968; my visits with Irma Thesleff and Lauri Saxén in Helsinki to learn about Nuclepore transfilter experimentation; my visits with Jean Victor Ruch, Robert Franck and their delightful colleagues in Strasbourg to learn about microdissection and heterologous tissue recombinations; my sabbatical with Geoff Burnstock in London at University College on Gower Street and the collaborations with Andrew Lumsden and Allan Davies on trigeminal ganglia cultures in serumless medium; my sabbatical with Michael Silbermann in Haifa, and my visits with Danny Deutsch in Jerusalem and Steve Weiner and Wolfie Traub in Rehovot, Israel; learning about immunocytochemistry from Moise Bendayan and Tony Nanci in Montreal; my visits to Sendai with Mas Nakamura and Yas Sasano; and my visits to Oaxaca, Mexico and the discoveries at Monte Alban related to craniofacial dysmorphogenesis. I believe that "in person" human interactions, sharing and learning, are imperatives for global scientific advances and to preserve the humanism in civilization!

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Selected References

Original Articles

SLAVKIN, H.C., BEIERLE, J. AND BAVETTA, L.A. (1968). Odontogenesis: cell-cell interactions *in vitro*. *Nature*: 217-269.

SLAVKIN, H.C. and BAVETTA, L.A. (1968). Organogenesis: prolonged differentiation and growth of tooth primordia on the chick chorioallantoic membrane. *Experientia 24:* 192-194.

SLAVKIN, H.C., BRINGAS, P., Jr., CAMERON, J.C., LEBARON, R. and BAVETTA, L.A. (1969). Epithelial and mesenchymal cell interactions with extracellular matrix material *in vitro*. *J. Embryol. Exp. Morphol. 22:* 395-405.

SLAVKIN, H.C., BRINGAS, P., Jr. and BAVETTA, L.A. (1969). Ribonucleic acid within the extracellular matrix during embryonic tooth formation. *J. Cell Physiol. 73:* 179-190.

SLAVKIN, H.C., FLORES, P., BRINGAS, P., Jr. and BAVETTA, L.A. (1970). Epithelial-mesenchymal interactions during odontogenesis. I. Isolation of several intercellular matrix low molecular weight methylated RNAs. *Dev. Biol. 23(2):* 276-296.

SLAVKIN, H.C., CROISSANT, R. and BRINGAS, P., Jr. (1972). Epithelial-mesenchymal interactions during odontogenesis. III. A simple method for the isolation of matrix vesicles. *J. Cell Biol. 53:* 841-849.

BONNER, J.J. and SLAVKIN, H.C. (1975). Cleft palate susceptibility linked to histocompatibility-2 (H-2) in the mouse. *Immunogenetics 2:* 213-218.

LEHMANN, R. and SLAVKIN, H.C. (1976). Localization of 'transcriptively active' cells during odontogenesis using acridine orange ultrastructural cytochemistry. *Dev. Biol. 49:* 438-456.

SLAVKIN, H.C. and BRINGAS, P., Jr. (1976). Epithelial-mesenchyme interactions during odontogenesis IV. Morphological evidence for direct heterotypic cell-cell contacts. *Dev. Biol. 50:* 428-442.

SLAVKIN, H.C., MINO, W. and BRINGAS, P., Jr. (1976). The biosynthesis and secretion of precursor enamel protein by ameloblasts as visualized by autoradiography after tryptophan administration. *Anat. Rec. 185(3):* 289-312.

LEE-OWN, V., ZEICHNER, M., BENVENISTE, K., DENNY, P., PAGLIA, L. and SLAVKIN, H.C. (1977). Cell-free translation of messenger RNAs of embryonic tooth organs: Synthesis of the major extracellular matrix proteins. *Biochem. Biophys. Res. Commun. 74(3):* 849-856.

SCHONFELD, S.E. and SLAVKIN, H.C. (1977). Demonstration of enamel matrix proteins on root-analogue surfaces of rabbit permanent incisor teeth. *Calcif. Tissue Res. 24:* 223-229.

BONNER, J.J., TERASAKI, P.I., THOMPSON, P., HOLVE, L.M., WILSON, L., EBBIN, A.J. and SLAVKIN, H.C. (1978). HLA phenotype frequencies in individuals with cleft lip and/or palate. *Tissue Antigens 12:* 228-232.

HATA, R. and SLAVKIN, H.C. (1978). *De novo* induction of a gene product during heterologous epithelial-mesenchymal interactions *in vitro*. *Proc. Natl. Acad. Sci. USA 75(6):* 2790-2794.

SLAVKIN, H.C., SLAVKIN, M.D. and BRINGAS, P., Jr. (1980). Mineralization during long-term cultivation of chick embryos *in vitro*. *Proc. Soc. Exp. Biol. Med. 163:* 249-257.

YAMADA, M., BRINGAS, P., JR., GRODIN, M., MacDOUGALL, M. and SLAVKIN, H.C. (1980). Developmental comparisons of murine secretory amelogenesis *in vivo*, as xenografts on chick chorio-allantoic membrane, and *in vitro*. *Calcif. Tissue Int. 31:* 161-171.

ZEICHNER-DAVID, M., WELIKY, B.G. and SLAVKIN, H.C. (1980). Isolation and preliminary characterization of epithelial-specific messenger ribonucleic acids and their products during embryonic tooth development. *Biochem. J. 185:* 489-496.

BROWNELL, A.G., BESSEM, C.C. and SLAVKIN, H.C. (1981). Possible functions of mesenchyme cell-derived fibronectin during formation of basal lamina. *Proc. Natl. Acad. Sci. USA 78(6):* 3711-3715.

CUMMINGS, E., BRINGAS, P. Jr., GRODIN, M.S. and SLAVKIN, H.C. (1981). Epithelial-directed mesenchyme differentiation *in vitro* model of murine odontoblast differentiation mediated by quail epithelia. *Differentiation 20:* 1-9.

MELNICK, M., JASKOLL, T. and SLAVKIN, H.C. (1981). Corticosteroid-induced left palate in mice and H-2 haplotype material and embryonic effects. *Immunogenetics 13:* 443-450.

SLAVKIN, H.C., BRINGAS, P., Jr., CUMMINGS, E. and GRODIN, M.S. (1982). Initiation of quail and mouse mandibular chondrogenesis and osteogenesis in a serumless, chemically-defined medium. *Calcif. Tissue Int. 34:* 111-112.

SLAVKIN, H.C., ZEICHNER-DAVID, M., MacDOUGALL, M., BRINGAS, P., Jr., BESSEM, C. and HONIG, L.S. (1982). Antibodies to murine amelogenins: Localization of enamel proteins during tooth organ development *in vitro*. *Differentiation 23:* 73-82.

FERGUSON, M.W.J., HONIG, L.S., BRINGAS, P., Jr. and SLAVKIN, H.C. (1983). Alligator mandibular development during long-term organ culture. *In Vitro 19:* 385-393.

GREENBERG, G., BRINGAS, P., Jr. and SLAVKIN, H.C. (1983). The epithelial genotype controls the pattern of extracellular enamel prism formation. *Differentiation 25:* 32-43.

SLAVKIN, H.C., GRAHAM, E., ZEICHNER-DAVID, M. and HILDEMANN, W. (1983). Enamel-like antigens in hagfish: Possible evolutionary significance. *Evolution 37:* 404-412.

SNEAD, M.L., ZEICHNER-DAVID, M., CHANDRA, T., ROBSON, K.J.H., WOO, S.L.C. and SLAVKIN, H.C. (1983). Construction and identification of mouse amelogenin cDNA clones. *Proc. Natl. Acad. Sci. USA 80:* 7254-7258.

FERGUSON, M.W.J., HONIG, L.S. and SLAVKIN, H.C. (1984). Differentiation of cultural palatal shelves from alligator, chick and mouse embryos. *Anat. Rec. 209(2):* 231-249.

HONIG, L.S., SMITH, B.T., SLAVKIN, H.C. and DONAHUE, H.G. (1984). Influence of the major histocompatibility complex (H-2) on glucocorticoid-stimulated pulmonary surfactant synthesis in two congenic mouse strains. *Proc. Soc. Exp. Biol. Med. 176:* 419-425.

DAVIS, J.U., BRINGAS, P., Jr. and SLAVKIN, H.C. (1985). Quantitative localization of polystyrene microspheres following microinjection in the avian metencephalic neural crest pathway. *J. Craniofac. Genet. Dev. Biol. 5:* 11-19.

NANCI, A., BENDAYAN, M. and SLAVKIN, H.C. (1985). Enamel protein biosynthesis and secretion in mouse incisor secretory ameloblasts as revealed by high resolution immunocytochemistry. *J. Histochem. Cytochem. 33:* 1153-1160.

GLAZMAN, L., BRINGAS, P., Jr. and SLAVKIN, H.C. (1986). Comparison of trytophan-labeled constituents of developing rodent molar enamel matrix non-enamel occlusal cusp, Hertwig's epithelial root sheath and presumptive root furcation regions: light microscopic autoradiography. *J. Craniofac. Genet. Dev. Biol. 6:* 171-188.

BRINGAS, P., Jr., NAKAMURA, M., NAKAMURA, E., EVANS, J. and SLAVKIN, H.C. (1987). Ultrastructural analysis of enamel formation during *in vitro* development using chemically-defined medium. *Scan. Microsc. 1:* 1103-1108.

EVANS, J., BRINGAS, P., Jr., NAKAMURA, M., NAKAMURA, E., SANTOS, V. and SLAVKIN, H.C. (1988). Metabolic expression of intrinsic developmental programs for dentine and enamel biomineralization in serumless, chemically-defined, organotypic culture. *Calcif. Tissue. Int. 42:* 220-230.

SLAVKIN, H.C., BESSEM, C., BRINGAS, P., Jr., ZEICHNER-DAVID, M., NANCI, A. and SNEAD, M.L. (1988). Sequential expression and differential function of multiple enamel proteins during fetal, neonatal and early postnatal stages of mouse molar organogenesis. *Differentiation 37:* 26-39.

SNEAD, M.L., LUO, W., LAU, E.C. and SLAVKIN, H.C. (1988). Spatial- and temporal-restricted pattern for amelogenin gene expression during mouse molar tooth organogenesis. *Development 104:* 77-85.

SLAVKIN, H.C., BESSEM, C., FINCHAM, A.G., BRINGAS, P., SANTOS, V., SNEAD, M.L. and ZEICHNER-DAVID, M.(1989). Human and mouse cementum proteins immunologically related to enamel proteins. *Biochim. Biophys. Acta 991:* 12-18.

SLAVKIN, H.C., BRINGAS, P., BESSEM, C., SANTOS, V., NAKAMURA, M., HSU, M., SNEAD, M.L., ZEICHNER-DAVID, M. and FINCHAM, A.G. (1989). Hertwig's epithelial root sheath differentiation and Initial cementum and bone formation during long-tern organ culture of mouse mandibular first molars using serumless, chemically-defined medium. *J. Periodont. Res. 23:* 28-40.

SLAVKIN, H.C., BRINGAS, P., Jr., SASANO, Y. and MAYO, M. (1989). Early embryonic mouse mandibular morphogenesis and cytodifferentiation in serumless, chemically-defined medium: A model for studies of autocrine and/or paracrine regulatory factors. *J. Craniofac. Genet. Dev. Biol. 9:* 185-205.

SASANO, Y., KIKUNAGA, S. and SLAVKIN, H.C. (1990). Development of embryonic mouse mandible in serumless, chemically-defined organ culture: morphogenesis and growth factors. *Tissue Culture 16:* 424-429.

KRESJA, R.J., BRINGAS, Jr., P. and SLAVKIN, H.C. (1991). The cyclostome model: an interpretation of conodont element structure and function based on cyclostome tooth morphology, function and life history. *Cour-Forsch-Inst Senckenberg 118:* 473-492.

LAU, E.C., SIMMER, J.P., BRINGAS, Jr., P., HSU, D.D-J., HU, C-C., ZEICHNER-DAVID, M., THIEMANN, F., SNEAD, M.L., SLAVKIN, H.C. and FINCHAM, A.G. (1992). Alternative splicing of the mouse amelogenin primary RNA transcript contributes to amelogenin heterogeneity. *Biochem. Biophys Res. Commun. 188:* 1253-1260.

MacDOUGALL, M., ZEICHNER-DAVID, M., MURRAY, J., CRALL, M., DAVIS, A. and SLAVKIN, H.C. (1992). Dentin phosphoprotein gene locus in not associated with dentinogenesis imperfecta type II and III. *Am. J. Hum. Genet. 50:* 190-194.

MAYO, M.L., BRINGAS, P., SANTOS, V., SHUM, L. and SLAVKIN, H.C. (1992). Desmin expression during early mouse tongue morphogenesis. *Int. J. Dev. Biol. 36:* 255-263.

SETH, R., SHUM, L., WU, F., WUENSCHELL, C., HALL, F.L., SLAVKIN, H.C. and WARBURTON, D. (1993). Role of epidermal growth factor expression in early mouse embryo lung branching morphogenesis in culture: antisense oligodeoxynucleotide inhibitory strategy. *Dev. Biol. 158:* 555-559.

DIEKWISCH, T., DAVID, S., BRINGAS, P., SANTOS, V. and SLAVKIN, H.C. (1993). Antisense inhibition of AMEL demonstrates supramolecular controls for enamel HAP crystal growth during embryonic mouse molar development. *Development 117:* 471-482.

SHUM, L., SAKAKURA, Y., BRINGAS, Jr., P., LUO, W., SNEAD, M. L., MAYO, M., CROHIN, C., MILLAR, S., WERB, Z., BUCKLEY, S., HALL, F.L., WARBURTON, D. and SLAVKIN, H.C. (1993). EGF abrogation induced fusilli-form dysmorphogenesis of Meckel's cartilage during embryonic mouse mandibular morphogenesis *in vitro. Development 118:* 903-917.

SLAVKIN, H.C. (1993). Rieger syndrome revisited: experimental approaches using pharmocologic and antisense strategies to abrogate EGF and TGF-α functions resulting in dysmorphogenesis during embryonic mouse craniofacial morphogenesis. *Am. J. Med. Genet. 47:* 689-697.

CHAI, Y., MAH, A., CROHIN, C., GROFF, S., BRINGAS, P., LE, T., SANTOS, V. and SLAVKIN, H. C. (1994). Specific transforming growth factor-beta subtypes regulate embryonic mouse Meckel's cartilage and tooth development. *Dev. Biol. 162:* 85-103.

SIMMER, J.P., LAU, E.C., HU, C.C., BRINGAS, P., SANTOS, V., AOBA, T., LACEY, M., NELSON, D., ZEICHNER-DAVID, M., SNEAD, M.L., SLAVKIN, H.C. and FINCHAM, A.G. (1994). Isolation and characterization of a mouse amelogenin expressed in *Escherichia coli. Calcif. Tissue Int. 54:* 312-319.

Chapters in Books

GREULICH, R.C. and SLAVKIN, H.C. (1965). Amino acid utilization in the synthesis of enamel and dentin matrices as visualized by autoradiography. In *The Use of Radioautography in Investigating Protein Synthesis* (Eds. C.P. Leblond and K.B. Warren). Academic Press, New York, pp. 199-214.

SLAVKIN, H.C. (1970). Cell aggregation: molecular specificity in outer cell surface materials. In *Phylogeny of Transplantation, Transplantation Proceedings* (Supplement) (Eds. W.H. Hildemann and E.L. Cooper) 11: 199-201.

SLAVKIN, H.C. (1971). The dynamics of extracellular and cell surface protein interactions. In *Cellular and Molecular Renewal in the Mammalian Body* (Eds. I.L. Cameron and J.D. Thrasher). Academic Press, New York, pp. 221-275.

SLAVKIN, H.C. and CROISSANT, R. (1973). Intercellular communication during odontogenesis epithelial-mesenchymal interactions: Isolation of extracellular matrix vesicles containing RNA. In *The Role of RNA in Reproduction and Development* (Eds. M.C. Niu and S. Segal). North Holland Publishing Co., Amsterdam, pp. 247-258,

SLAVKIN, H.C. (1975). The isolation and characterization of calcifying and non-calcifying matrix vesicles from dentine. In *International Colloquium on Physical Chemistry and Crystallography of Apatites of Biological Interest* (ed. G. Montel). Centre National de la Recherche Scientifique, Paris, pp. 161-177.

SLAVKIN, H.C., TRUMP, G.N., BROWNELL, A.G. and SORGENTE, N. (1977). Epithelial-mesenchymal interactions: mesenchymal specificity. In *Cell and Tissue Interactions* (Eds. J.W. Lash and M.M. Burger). Raven Press, New York, pp. 29-46.

SLAVKIN, H.C., CROISSANT, R., GUENTHER, H.G. and SORGENTE, N. (1978). The role of matrix vesicles in mineralization and calcification. In *Formation and Calcification of Hard Tissues* (Eds. R.V. Talmage and H. Ozawa). Shakai Hoken Publishing Company, Ltd., Tokyo, pp. 59-82

SLAVKIN, H.C. (1979). Overview of research on craniofacial malformations: Gene regulation. In *Second International Conferences on the Diagnosis and Treatment of Craniofacial Anomalies* (Ed. J.M. Converse). The C.V. Mosby Company, St. Louis, pp. 68-81.

SLAVKIN, H.C. (1979). Speculations regarding the influence of the major histocompatibility complex (H-2) upon congenital craniofacial malformations in inbred and congenic strains of mice. In *Craniofacial Dysmorphology: Understanding the Clinical Dilemna Through Developmental Biology, Birth Defects: Original Article Series* Vol. XV (Ed. M. Melnick). Alan R. Liss, Inc., New York, pp. 43-54

SLAVKIN, H.C. and ZEICHNER-DAVID, M. (1981). The possible mode of transmission for 'inductive RNA' during epithelial-mesenchymal interactions. In: *The Role of RNA in Reproduction and Development* (Eds. M.C. Niu and C. Hsiao-hui). Science Press (Beijing) and Van Nostran Reinhold Co. (New York), pp. 686-713.

FERGUSON, M.W.J., HONIG, L.S., BRINGAS, P., Jr. and SLAVKIN, H.C. (1982). *In vivo* and *in vitro* development of first branchial arch derivatives in Alligator mississippiensis. In *Factors and Mechanisms Influencing Bone Growth* (Eds. A.D. Dixon and B.G. Sarnat). Alan R. Liss, Inc., New York, pp. 275-286

SLAVKIN, H.C., CUMMINGS, E., BRINGAS, P., Jr. and HONIG, L.S. (1982). Epithelial-derived basal lamina regulation of mesenchymal cell differentiation. In *Embryonic Development: Part B: Cellular Aspects* (eds. M.M. Burger and R. Weber). Alan R. Liss, Inc., New York, pp. 249-259

SLAVKIN, H.C., ZEICHNER-DAVID, M., FERGUSON, M., TERMINE, J.D., GRAHAM, E., MacDOUGALL, M., BRINGAS, P., Jr., BESSEM, C. and GRODIN, M. (1982). Phylogenetic and immunogenetic aspects of enamel proteins. In *Oral Immunogenetics and Tissue Transplantation* (Eds. G.R. Riviere and W.H. Hildemann). Elsevier/North Holland Publishers, New York, pp. 241-251

SLAVKIN, H.C. (1984). Morphogenesis of a complex organ: Vertebrate palate development. In *Current Topics in Developmental Biology*, Vol. 19 (Ed. E.F. Zimmerman). Academic Press, New York, pp. 1-16.

SLAVKIN, H.C., SNEAD, M.L., ZEICHNER-DAVID, M., BRINGAS, P., Jr. and GREENBERG, G.L. (1984). Amelogenin gene expression during epithelial-mesenchymal interactions. In *The Role of Extracellular Matrix in Development* (Ed. R.L. Trelstad). Alan R. Liss, Inc., New York, pp. 221-253

SLAVKIN, H.C., SNEAD, M.L., ZEICHNER-DAVID, M., MacDOUGALL, M., FINCHAM, A., LAU, E.C., LUO, W., NAKAMURA, M., OLIVER, P. and EVANS, J. (1988). Factors influencing expression of dental ECM biomineralization. In *Cell and Molecular Biology of Hard Tissues, CIBA Foundation Symposium 135* (Eds. G. Rodan and A. Caplan). John Wiley and Sons, Chichester (UK), pp. 22-41.

SLAVKIN, H.C. (1990). Cellular and molecular determinants during craniofacial development. In *Craniofacial Malformations: Embryology, Classification, Surgery* (Eds. M. Stricker, J. Van der Meulen, B. Raphael and R.F. Mazzola). Livingstone Publishers, London, pp. 1-20

SLAVKIN, H.C. (1991). Future Prospects for Craniofacial Molecular Biology in the 1990s. In *Craniofacial Growth Series* (from Symposium on Craniofacial Growth) (Ed. D. Carlson and A. Ferrara). University of Michigan Press, Ann Arbor, pp. 179-202.

SLAVKIN, H.C. (1991). Perspectives on morphogenesis. In *Fundamentals of Bone Growth: Methodology and Applications* (Eds. A.D. Dixon and B.G. Sarnat). CRC Press, Boca Raton, pp. 23-34

SLAVKIN, H.C., KRESJA, R.J., FINCHAM, A.G., BRINGAS, P., SANTOS, V., SASANO, Y., SNEAD, M.L. and ZEICHNER-DAVID, M. (1991). Evolution of enamel proteins: a paradigm for mechanisms of biomineralization. In *Mechanisms of Biomineralization* (Eds. S. Suga and H. Nakahara). Springer-Verlag, Tokyo, pp. 383-389.

SLAVKIN, H.C., HU, C.C., SAKAKURA, Y., DIEKWISCH, T., CHAI, Y., MAYO, M., BRINGAS, Jr., P., SIMMER, J., MAK, G., SASANO, Y. and SASSON, D. (1992). Gene expression, signal transduction and tissue-specific biomineralization during mammalian tooth development. In *Critical Review in Eucaryotic Gene Expression* (Eds. G.S. Stein, J.L. Stein and J.B. Lian). CRC Press, Inc., pp. 315-329.

CHAI, Y. and SLAVKIN, H.C. (1994). Bone Induction. In *Oral and Maxillofacial Surgery Clinics of North America*, (Eds. W. Howard Davis and H. Sailer). W.B. Saunders Company, Philadelphia, pp. 739-753.

GORLIN, R. J. and SLAVKIN, H. C. (In press). Embryology of the face. In *Congenital Anomalies in Otolaryngology* (Eds. T.L. Tewfik and V. Der Kaloustian). Oxford Press, London.

SLAVKIN, H. C. (In press). Recombinant DNA technology in the diagnosis and therapeutics of oral medicine. In *DNA, The Double Helix Forty Years: Perspective and Prospective* (Ed. D. Chambers) Ann. New York Acad. Sci.

Books and Monographs

SLAVKIN, H.C. (1972). *Comparative Molecular Biology of Extracellular Matrices.* Academic Press, New York.

SLAVKIN, H.C. and BAVETTA, L.A. (1972). *Developmental Aspects of Oral Biology.* Academic Press, New York.

SLAVKIN, H.C. (1974) Tooth Formation: A Tool in Developmental Biology. *Oral Sciences Reviews 4:* 1-120.

SLAVKIN, H.C. and R.C. GREULICH (1975). *Extracellular Matrix Influences on Gene Expression.* Academic Press, New York.

SLAVKIN, H.C. and D.W. COHEN (1979). *Current Advances in Oral Biology* (a 12-volume series). University of Pennsylvania Press, Philadelphia.

SLAVKIN, H.C. (1979). Developmental Craniofacial Biology. Lea and Febiger, Philadelphia.

SLAVKIN, H.C., ZEICHNER-DAVID, M. and SIDDIQUI, M.A.Q. (1981). Molecular aspects of tooth morphogenesis and differentiation. *Molecular Aspects of Medicine 4:* 125-188.

PRUZANSKY, S. and SLAVKIN, H.C. (1982). An evaluation and assessment of the state of the science: Congenital and acquired craniofacial malformations. *U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.*

SILBERMANN, M. and H.C. SLAVKIN (1982). *Current Advances in Skeletogenesis Development, Biomineralization, Mediators and Metabolic Bone Disease.* Excerpta Medica, Amsterdam.

SLAVKIN, H.C. and PRICE, P. (1992). *Chemistry and Biology of Mineralized Tissues.* Elsevier Scientific Publishers, Amsterdam.