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# **Bernhard Guggenheim – Critical Mind at The Forefront of Oral Microbiology**

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## **Abstract**

Bernhard Guggenheim is a distinguished leader in oral microbiology and immunology and a recipient of many honors. This article outlines his background, his scientific career and illuminates some of his important contributions to dental research. At the age of 75 he continues to scrutinize established paradigms and unremittingly fosters demanding biofilm research.

It was in late summer of the year 1980 when I met Bernhard Guggenheim for the first time. I was a 31-year old postdoc trained in developmental biology who had just completed a 2 ½ year residence at the Wistar Institute in Philadelphia. When I arrived at the University of Zürich to engage in cancer immunology, I learned that the promised position had been cut due to restructuring and I was seriously questioning whether I would ever be able to support a young family of four by being a researcher and lecturer. Into the thick of my desperation a professor from the Dental Institute called and asked to meet me in the garden of a little bakery nearby. It was Bernhard Guggenheim ["Bernie" to all who knew him, except for the Swiss-German folks who call him "Guggi"]. Out of nowhere Bernie offered me a position as "Oberassistent": "You can start as soon as you want, you are free to choose your topics of research as long as they are related to oral microbiology and/or immunology. All I request is team spirit, openness and solidarity." I was flabbergasted by so much trust. Trust in somebody he did not know, somebody he had never seen before. Within a few minutes I had learned more about the man than many words can describe: a demanding, ambitious, supportive, sometimes short-spoken and brusque boss with an ability to take lightning quick decisions. A man who would always care for his staff, protect and help the members of his team in the middle of an often rough and pressured university environment. His visions and expectations reached sometimes beyond of what my colleagues and I considered realistically achievable, but all too often he was right.

## **FARMER GETTING INTO ORAL MICROBIOLOGY**

When I joined Bernhard Guggenheim's group he was already an internationally recognized scientist with an outstanding record in caries microbiology and immunology. Many might not know and will be astonished to learn from what kind of background he had started his illustrious career crowned by

prestigious honors such as the silver medal of the city of Paris, the IADR Research in Dental Caries Award, and honorary doctor degrees from the Universities of Umeå and Bergen. Guggi was born in Zürich into a poor Jewish family during frightening times, two years before the outbreak of World War II. He was raised by his mother, attended schools in Zürich, played passionately and quite successfully soccer in one of the best clubs of the country and spent much of his spare time in the renowned archive of Theo Pinkus, “a place of pilgrimage of the new left” (Anonymous, 1991), studying the history of the Worker’s Movement in Europe during the first half of the 20th century. However, his opinions created problems at school and he was forced to leave grammar school for political reasons. Inspired in part by the idea to join a Kibbutz he did an apprenticeship at the “Strickhof” – the farm and agricultural school of the state of Zürich. But then, denied to further follow his plans, young Bernie made up his “Matura” (the final grammar school exam), enrolled at the Swiss Federal Institute of Technology (ETH) to study agriculture, and, four years later, was awarded the Silver Medal of ETH for his excellent diploma thesis. To this day, his affection to nature remains a focal point of his life. It surfaces for example during the morning coffee breaks when he enthusiastically talks about hunting, collecting mushrooms, breeding bee colonies, or his success in growing orchids, roses, apricots and many other products in his garden. But what had all this to do with dentistry? Bernie decided 1961 to continue his education with a PhD at the ETH under the guidance of Profs. Leopold Ettlinger (a microbiologist) and Edzard Zollikofer (an agronomics engineer) (Guggenheim, 1966). For the experimental part of his thesis he joined the Caries Research Unit of the Dental Institute of the University of Zürich, which was directed by Hans R. Mühlemann. In Hans Mühlemann he encountered a brilliant, charismatic teacher who was one of the leading oral scientists at the time and the head of young enthusiastic team of researchers that included such future “heavy weights” as Hubert Schroeder, Klaus König, Peter Hotz, or Paul Stöckli at the start of their distinguished careers. Many discussions with Bernie illustrated what an inspiring, contagious, unrestricted, and yet highly ambitious atmosphere had characterized the Dental Institute at that time. He was sent abroad to the labs of Paul Keyes and particularly Ron Gibbons and Sig Socransky at the Forsyth Dental Center in Boston and quickly learned to know the most distinguished oral biologists of the last 50 years. The photograph in Figure 1 shows Bernie hidden behind dark sunglasses in the middle of his illustrious colleagues at the NIDR sponsored Dental Plaque Conference in 1975. Many of these young energetic researches had their fights with the research establishment of the time, resulting amongst other things in the foundation of the European Group of Oral Biology (ERGOB). Starting out as a form of protest against

the 10-minute-paper frame of most conferences organized by the established research societies, ERGOB aimed at organizing with minimum time and effort informal research meetings of not more than a dozen experts for the free exchange of ideas and fresh information. The only regular participants were Bernie and Ole Fejerskov, for 30 years president and treasurer of the organization, respectively, and a representative of the company (-ies) providing the necessary financial support. The history of ERGOB is full of highlights and anecdotes, the narration of which would unfortunately blow the format of this article. Unforgettable for any who ever had the chance to be invited to one of these meetings were besides the scientific quality certainly the exquisite dinners offered by the host, testimony to the generous connoisseur of fine food and wine that Bernie is. Who would have thought at the time that 44 years later ERGOB still continues to play an important role in the free exchange and promotion of innovative research concepts in oral biology?

#### **QUICK CAREER**

At the age of 35, just 10 years after starting his PhD thesis, Bernie was elected Professor and head of a newly founded, independent section of the Dental Institute, the Oral Microbiology and General Immunology department. Apparently his excellent research on glucosyltransferases, extracellular polysaccharides (EPS) of cariogenic streptococci, and EPS-degrading enzymes (Guggenheim *et al.*, 1966; Guggenheim and Schroeder, 1967; Guggenheim and Newbrun, 1969; Guggenheim and Haller, 1972), his networking abilities, and certainly his highly visible presence at national and international conferences had paid dividends. His presence at meetings mirrors another facet of Bernie's personality which one reviewer of this article characterized so tellingly in writing: "Any person who presented sloppy data could expect to hear from Bernie in clear and unambiguous terms. ... Bernie never shied away from controversy; in fact I am sure he welcomed participating. ... It could be said safely that Bernie wasn't always right but most assuredly he was never in doubt."

With the establishment of an own independent research group and influenced by the enormous progress of experimental immunology in the early 1970s, Bernie and his senior assistant and immunologist Johann Jakob Burckhardt started to broaden the focus of their research to periodontal diseases and engaged in complex analyses of the T cell response in rats that had been associated with *Streptococcus mutans/sobrinus* and/or *Actinomyces viscosus*. Unfortunately their hopes to identify the etiologically important bacterial virulence factors and to learn to understand the specific cellular host response against them turned out to be an elusive goal. Instead it became clear that the

predominant T cell reaction was mitogen-driven and not, as expected, strictly antigen-specific. But, the T cell response was impressively powerful as evidenced in an *in vitro* model of periodontal tissue destruction by the killing of syngeneic fibroblasts. Interestingly, the driving forces behind this *A. viscosus* dependent cytotoxicity were unspecifically elicited soluble factors (nowadays known as lymphokines) that in turn had activated T lymphocytes and possibly macrophages to become cytotoxic to fibroblasts (Gaegauf-Zollinger *et al.*, 1982).

## **EXPANSION TO PERIODONTAL RESEARCH**

In 1981 Bernie returned from a conference, probably the “5th International Conference on Periodontal Research”, and reported enthusiastically about new black pigmented *Bacteroides* species, the new species *Bacteroides forsythus*, the revival of *Actinobacillus actinomycetemcomitans* (Aa), the ever elusive spirochetes, which all were obviously strongly associated with forms of progressive periodontal disease. The specific plaque hypothesis was re-born; studies of these putative pathogens and of the antibody response elicited by them promised to provide new diagnostic tools to judge the risk for disease progression. New, scientifically based treatments that could replace old-fashioned scaling and root planning seemed to appear on the horizon. In retrospective, it is fascinating to see how much these developments had influenced Bernie and his young newly recruited co-workers Gaby Allenspach-Petrzilka, Peter Schüpbach, Chris Wyss and the author of this article in the design of their research activities during the years to come: In analogy to the most successful efforts of the 60s and 70s with caries rat models, Bernie and his life-long friend Rudolf Schmid put a lot of effort into the development of rat models for periodontal disease that, however, for a variety of reasons should never prove as rewarding as expected. Gaby Allenspach studied bacterial invasion of the periodontal tissues – quite a controversial issue already at the time. Chris Wyss devoted all his know-how and energy to the cultivation of presumably “uncultivables” from the oral cavity. Several new species of spirochetes (e.g. Wyss *et al.*, 1999) and a series of sophisticated culture media (e.g. Wyss, 1992) are the result of this masterful work. Further, Bernie and the author investigated the host’s antibody response to Aa, *Porphyromonas gingivalis*, and *Prevotella intermedia* (*Bacteroides gingivalis* and *Bacteroides intermedius* at the time), but contrary to our expectations, had to conclude that high titers reflected mere colonization by the target organisms at one point in time, rather than bearing valuable information on disease activity or risk for progression (Gmür *et al.*, 1986). In yet another line of research we studied the composition of subgingival plaque by target-specific fluorescence microscopy

using numerous monoclonal antibodies from our own production [many of which are now available at the Developmental Studies Hybridoma Bank of the University of Iowa; <http://dshb.biology.uiowa.edu/>] and, less laborious, 16S rRNA fluorescent *in situ* hybridization probes. The results lead us quickly to contradict the specific plaque hypothesis as we realized that all the putative periodontal pathogens were in fact commensal organisms that could be detected in lower numbers interproximally, in stable pockets, or in supragingival plaque as well (Gmür *et al.*, 1989; Gmür and Guggenheim, 1994). Instead with exogenous pathogens one had to deal with opportunistic organisms expanding greatly in the subgingival space owing to their unique ability to withstand and bypass the aggressive host response.

### **A LEADER IN THE BOOMING FIELD OF BIOFILM RESEARCH**

For much of the first 30 years of his career as a scientist in the field of oral microbiology Bernie and his group had the privilege to work in a land of plenty in terms of financial support by the university. What was needed for successful research was available. But he was quick to realize in the mid 1990s that things were about to change and optioned to intensify in certain fields of his research the collaboration with the interested industry. One such collaboration, dealt with a promising milk casein compound that could strongly inhibit the colonization of pellicle-coated enamel by *Streptococcus sobrinus* (Guggenheim *et al.*, 1999). However, when applied to rat caries models or to *in situ* validation it failed to yield the anticipated degree of a caries-preventing effect. Bernie's conclusion was that under *in vivo* conditions bacterial growth will rapidly compensate reduced initial colonization and therefore he figured that instead of testing a potentially interesting compound with planktonic bacteria in the absence of growth, one has to work with biofilm model systems that can mimic to a certain extent the native ecologies defining microbial life in the oral cavity. The concept for the "Zurich biofilm model" was born. At the time, Bernie called for a lab meeting, explained his conclusions, and urged his group to unite efforts in creating this model. He clearly foresaw the scientific potential of this new approach and not least the potential for generating the urgently needed third-party funding support. With André Meier as his precious right-hand in the lab, Thomas Thurnheer, Stuart Shapiro, and the author, to mention just a few of Bernie's coworkers, a series of highly reproducible *in vitro* multi-species biofilm models were created that quickly gained broad international recognition (Shapiro *et al.*, 2002; Thurnheer *et al.*, 2003; Guggenheim *et al.*, 2004; Guggenheim *et al.*, 2011). They were further advanced in recent years culminating in the most complex construction of *in vitro* "subgingival" biofilms

that for the first time allow for the modeling of host-pathogen interactions (Guggenheim *et al.*, 2009; Belibasakis *et al.*, 2011; Zijngel *et al.*, 2012).

## **DEDICATION TO THE ADVANCEMENT OF PREVENTIVE DENTISTRY AND CLINICAL HYGIENE**

This article would not be accurate without giving consideration to the great merits Bernhard Guggenheim had and still has in both the advancement of preventive dentistry and of clinical hygiene management. The two basically unrelated activities had their onset in the early 1980's. At that time Bernie initiated, together with a couple of colleagues representing the other three university dental centers of Switzerland, the so called "Aktion Zahnfreundlich", in English words the "tooth-friendly society", a superbly designed effort to promote the use of sugar substitutes in any form of confectionaries in order to reduce the incidence of caries and to implant within the population a personal consciousness for improved caries preventive behavior. To this end the Toothfriendly logo (Figure 2) was created as a seal of quality for products, which are safe for teeth.

Toothfriendliness of any product had to be demonstrated experimentally with humans by product-specific plaque-pH telemetry testing (Imfeld, 1983). The "tooth-friendly society" would explain and popularize the campaign; the industry would provide the financial support. Bernie was the driving force behind the new association and acted for >20 years as its president. Within a few years the little logo could be found on the wrapping of nearly every product with sugar substitutes sold in Switzerland and more than 90% of the population became familiar with the meaning of the little "tooth-goblin" with his umbrella. The idea spread to other countries (e.g. Germany, Japan, Korea, Turkey, Thailand) and continues to expand under the guidance of "Toothfriendly International" (<http://www.toothfriendly.ch>), although progress has slowed down in recent years for various complex reasons.

Bernie's efforts to engage in the improvement of clinical hygiene resulted from a feeling of faint and responsibility vis-à-vis of the threat that emerging HIV epidemic put onto the dental profession. Being the head of Oral Microbiology and Immunology he was responsible for clinical and laboratory hygiene at the Dental Institute of the University of Zürich. Hence, he was directly confronted with the increasing influx of high-risk patients and the fears of the dental personnel to sustain a life threatening infection. He quickly realized that better anamnesis and segregation of HIV+ and high-risk patients will only have counterproductive effects and consequently advocated, often against the conviction of the senior dentists, that all patients must be treated equally regardless whether information on their risk status was known or not. Bernie took the lead in reforming the hygiene standards of clinical practice in

Switzerland in designing and implementing the new clinical facilities at the University Dental Center and, together with support from the industry, developed and fine-tuned new equipment for the safe cleaning and maintenance of dental instruments, e.g. the fully automated processing of hand-pieces. Till today Bernie serves in the board of the Swiss Dental Association that establishes the guidelines for the hygiene standards of clinical dentistry in Switzerland.

## **RETIREMENT – CHANCE TO REINFORCE RESERACH**

Of course there are many other important achievements that could not be mentioned in this short appraisal, for example Bernie's tenure as the dean of the dental center, or his role as a teacher of more than 1300 dentists now active in all parts of Switzerland. At the age of 75 he is still active, visits his little office almost daily and is full of ideas for new experiments. A particularly difficult one is specially important to him and ranks among the top scientific questions he has addressed in his long scientific career: the proof that microbial colonization of the oral cavity is less a problem of specific adherence as taught by the current textbooks, but is defined ecologically by the organism's ability to proliferate.

## **ACKNOWLEDGEMENTS**

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**Figure 1. Researcher reunion at the NIDR sponsored Dental Plaque conference 1975.**

Kneeling (left to right): Ernest Newbrun, Walter Loesche, Harald L e, Robert Genco, Thomas Valega.  
Standing (left to right): Paul Keyes, unknown, Ronald Gibbons, Sigmund Socransky, Roy Page,  
William Bowen, Anthony Rizzo, Thomas Temple, Jan Carlsson, James English, John Goggins,  
Bernhard Guggenheim, Max Listgarten, William McHugh, Robert Fitzgerald. Photograph courtesy  
of ..... Reproduced with permission of ..... Gary C. Armitage published this photograph in  
a recent review (Armitage and Robertson, 2009) from which parts of this figure legend were adopted.



**Figure 2. The Toothfriendly logo**

The Toothfriendly logo was created in 1982 on an initiative of the Swiss University Dental Faculties to distinguish products that are safe to teeth, i.e. are non-cariogenic and non-erosive. These "toothfriendly" properties are determined in a standardized *in vivo* plaque-pH telemetry test conducted by independent University Dental Institutes. (Source: <http://www.toothfriendly.ch>)

