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# Living History-Biography: From Oral Pathology to Craniofacial Genetics

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### Early Life

I was born on 11 January 1923 in Hudson, N.Y., the only child of James Alter Gorlin and Gladys Gretchen Hallenbeck. Abandoned by my mother, my father placed me in the care of my great aunt who raised me until I was 11 years old when she began to suffer ill health and had no more economic wherewithal to support me further. I then joined my father and my stepmother whom he had recently married. My father was a small scale businessman with little formal education. We moved several times within a few years to small towns in New Jersey, partly the result of his poor business acumen and partly due to malencounters with the law. In 1937, we moved to Newark and settled in a two-bedroom apartment with grandparents, uncles, aunts, cousins, and two boarders. In spite of the crowded conditions, every niche and recess being occupied by a bed, it was not, to the best of my memory, an unhappy home.

I do not know what hopes or ambitions my father and stepmother had for me. They respected education but they believed that since they were so impecunious, college was out of the picture. After I rejected the idea of becoming a priest (my stepmother's brother's calling), my father suggested that I take a General Business Preparation curriculum in high school. It was after a year of such training that I moved to Newark. A high school General Science teacher recognized some bizarre talent in me and requested that I should take a College Preparation course. This, I did, after much discussion with my parents, who remained skeptical concerning future finances. The switch to such a different curriculum was somewhat painful but I seemed to find science courses enjoyable. Our finances were, in actuality, so shaky, my father then working on the WPA, that I was encouraged to seek an after-school job. I found one in a drug store where I started as a delivery boy but soon began to compound prescriptions. The neighborhood was remarkable. It was 70% Jewish and definitely upwardly mobile. Most of my friends were planning to go to college. I had read little outside of my required course work, but I scored well and managed to receive a scholarship to Columbia College in New York City.

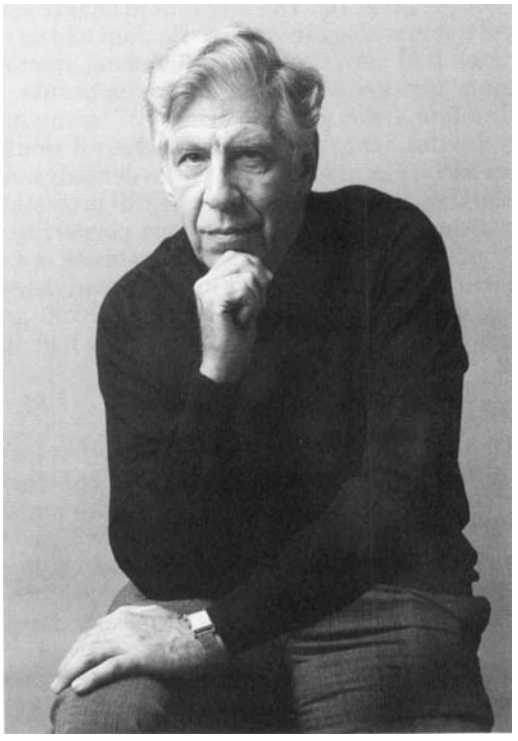

Fig. 1. Recent photograph of Robert J. Gorlin with signature.

That was a shock! There were clearly two classes of students—the rich and the poor—the dormitory dwellers and the commuters—the preppies and the public schoolers. But everyone seemed to know everything. They had read everything and I had read nothing. They had had courses in European history and Greek and Roman history and music and art and had read the great books and spoke languages like French and German and could read Latin and ancient Greek with ease. And they were articulate and charming. It took me almost a year

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of commuting two hours each way on bus, train, and subway trying to unravel the mystery of why they were so smart and I was so illiterate. By husbanding what few resources I had and cadging as many extra dollars as I could by creating a "corsage agency" for fraternity dances, and running a "personal stationery agency," and a "personal laundry service," I managed to float an education (tuition was $400/yr, room was $5/week, and

Receiving my A.B. in three years with World War II in full flower, and knowing I would be drafted, I volunteered, was inducted, and was sent for basic training in Texas and assigned to Army Specialized Training Program (ASTP) at Texas A&M in civil engineering. After several months, we were told that the Army was going to phase out the program. The sergeant in charge asked us who had taken zoology in college. He then told us that so many men had been drafted that medical, dental, and veterinary colleges were begging for applicants. Being second in line, I was given a form for Washington University Dental School in St. Louis where I would continue in ASTP but now as a student in dentistry. Admittedly the thought of entering any health profession was not something that I had spent time pondering, but I knew that I did not like the physical isolation of a chemistry laboratory or being part of a highway surveying team (in Texas this was often done at 110°F) and the prospect of being returned to the troops had limited appeal.

## Dental School

It didn't take me very long to recognize that I was not God's gift to dentistry. While I enjoyed the basic sciences, the idea of running a private practice was frightening. When it came to business, as many of my astute classmates informed me, I couldn't make change in a drug store. In my second year, I had the good fortune to be again saved by a remarkable teacher, Dr. Barnet M. Levy.

He taught me about microbiology, pathology, and oral pathology and protected dentistry from me. At the end of the second year, a few of us thought that perhaps we should try to transfer to medical school. The war was running down and rumor had it that the Army and Navy were going to drop the professional programs. We had no idea what would happen to us—whether we would be discharged or would be returned to the rank and file. Barnet Levy, who served as mentor to several of us, discouraged us from applying. He told us to consider graduate education following dental school, and to bolster his assertion that there was a future in this area, he pointed out the availability of two fellowship programs, one at the University of Rochester and the other at Columbia Presbyterian Medical Center. The latter offered $1,900 a year and the former $100 less, but one could enroll for a Ph.D. I applied for and received both, but I opted for Columbia because they said I could open a small practice in the dental clinic and garner a few additional dollars.

Somehow or other, I slogged through the clinical years, with Barney always coming to my defense, convincing the rest of the faculty that I would do little harm to the dental profession by being graduated. I seemed to have but a single talent—that of being a better than average diagnostician. I suspect that they looked the other way and signed my diploma because I was graduated in June 1947. I did not attend my ceremony but hightailed it for New York to take the N.Y. and N.J. dental state board exams and to begin my work at Columbia in medical and surgical pathology.

## Pathology Training

The years at Columbia Presbyterian (1947–1951) were happy ones in spite of my abject poverty. Nineteen hundred dollars didn't go far, even in those days. And my dental practice consisted of helping out even poorer medical students who needed teeth filled in the evenings. But in spite of hard times, I found myself in a field which I could comprehend and in which I could truly excel. Dr. Daniel Ziskin served as my mentor, but he soon fell ill of a retroperitoneal sarcoma and lived less than a year. However, during that year he convinced me that I could help develop the field of oral pathology. I needed but to get as much experience and training as I could pack into three years by attending courses and conferences in pathology, dermatology, dermatopathology, and medicine. There were no graduate courses given in oral pathology during those years. The undergraduate lectures consisted of about 7 hours delivered by Dr. Lester Cahn, but our contact was cursory as the time he spent at the medical pathology department was minimal. I was inspired by learning at the feet of Drs. Arthur Purdy Stout, Arthur Allen, and Raffaele Lattes. However, my most seminal experience at Columbia was hearing a single lecture by Dr. Helen Curth. That one experience had the most profound effect on my life, but more about that later.

After two years my economic base had miniscule improvement by joint appointment as Instructor in Medical Pathology at Columbia Presbyterian and as oral pathologist at the Bronx VAH.

## Greenland, Operation Blue Jay, and Economic Stability

After a year or two of splitting my time between Columbia and the Bronx VAH, I began to view the future with jaundiced eye. Many of my friends talked about great job offers, others had opened fine practices in medical or surgical pathology, orthodontics, dermatology, periodontics, etc. Several had gotten married and some even had children. I had not seen an advertisement for an oral pathologist, much less had the prospects of a permanent job that would ensure any sort of future. While I did date, I remember having had to discourage any serious prospects by telling them the truth about my bleak future.

Again, almost miraculously, the dean of the dental school called me to his office and related that the government was looking for someone who could establish a dental office, render emergency dental services, and establish a standard clinical medical laboratory at some undesignated overseas site. There seemed to be a lot of hush-hush about the project. I asked him if he could find out more about where it would be carried out. Several weeks elapsed and both of us had forgotten about the

project. Suddenly one morning, he called me, apologized for his delinquency, gave me an identifying letter, and instructed me to go to an address on lower Broadway where I was to be interviewed.

Upon presenting my credentials, I was surprised to see so many military brass. A civilian asked me if I was sufficiently interested to meet the medical director of what was to be known as Operation Blue Jay. The purpose of the mission was to create the DEW line, a circumpolar group of four radar bases which would give the United States and Canada about 35 minutes of early warning if Russian planes were to attack over the pole. The meeting with the Medical Director was to take place in Rosemount, MN. I flew to Minneapolis where I was met, vetted, brought to the logistics base, hired, and placed on a munificent annual salary of $23,600 minus cost of maintenance and taxes, netting me about $10,000. I never knew anyone who made that much! I was to be a plutocrat.

I spent several months in Rosemount, obtaining considerable aid from Dean William Crawford and a cadre of young faculty of the University of Minnesota Dental School in putting over 10,000 constructioneers in reasonable dental shape for their stay in Greenland. I understand that several of the younger faculty got their start in practice this way. The secretive nature of the project was dumbfounding, especially as intercontinental ballistic missiles were a reality which made the bases obsolete before they were created. But they were built anyway, the only surviving one, Thule, currently serving as a place where one can land if one's plane has trouble on the polar route.

The fact that I was temporarily leaving pathology didn't phase me. For only a year's servitude this was to be my salvation—or so I viewed it.

I left for Greenland by flying to Westover Air Force Base in July 1951 and from there to Goose Bay, Labrador, and then to Thule, located several hundred miles from the pole. Life was relatively easy. Until the Davis Strait froze in September I lived aboard ship and used real dental equipment, but soon was transferred to a Nissen hut which looked like a loaf of bread with double doors at both ends until our permanent quarters were built on strong insulated supports to prevent heat transfer as the permafrost, consisting of earth and ice crystals, would melt. I was astonished to see essentially a small village erected within weeks.

After several months, I elected to go on vacation. One of the constructioneers had been killed in a tractor accident, and I accompanied his body to the States. From there, I went to Panama aboard ship with a childhood friend who served as ship's doctor. In Panama, I gorged myself on tropical fruits and succulent oysters and returned to New York where I had the wonderful fortune of meeting my future wife, Marilyn Alpern, who was employed at that time by Warner Brothers in their story-talent department.

After a few dates (Westminster Kennel Club, a Broadway play), I retraced my steps to Greenland—feeling very Faustian for having sold my soul for a handful of pottage. Within two weeks, I began to turn yellow. Hepatitis type A became an obvious diagnosis and I was washed out after being returned to Westover Air Force Base.

Somehow or other, I managed to drag myself to the Bronx VAH for three month's hospitalization due to stubbornly lagged liver functions. It was there that I openly courted my future wife. She visited at least three times a week, and as soon as I was discharged we were married.

### Iowa and the Navy Years

It was déjà vu poverty. Only now, I was married, poor, and without a job. Again, it was Barney Levy who proffered a solution. Iowa needed someone to teach medical pathology to dental students. I phone Dr. Alton K. Fisher who hired me on the spot at $5,000. During that tenure I honed my lecturing skills and decided to enroll for an M.S. in physical organic chemistry. Why, I will never know! My wife and I lived in a Quonset hut, a relic of WWII, situated on a golf course. Sybaritic it wasn't. But it was home and my wife made it a delight to come to at evening's end.

About 4 months before I was to obtain my degree, I received a note from the friendly doctors' draft board beckoning me back into service. It seems that I had served one month less than two years in WW II and they needed me for two years more. This time, I volunteered for the Navy—why shouldn't they suffer too?—and received orders for Great Lakes Naval Training Station.

The Navy soon recognized that I possessed greater legal then operative dental skills. Observed doing dentistry in my black socks and overheard employing my own nomenclature for dental instruments—"Pookie, would you hand me a double bombo for this single frackle?" I was clearly guilty of unNaval-like behavior! I did some oral surgery, but as they had a regular Navy man doing that, they sent me to Courts and Boards to put teeth in the law. The Uniform Code of Justice is not complicated and I had it mastered in short order to prosecute, defend, and judge such heinous crimes as being AWOL, bringing 3.2 beer aboard base, being caught in the sack with a WAVE, and failing to obey the order of a noncom.

As I often set the docket, I attended court every other day—between trips to the hobby shop where I made furniture. After almost two years, the Navy and I parted ways, neither the worse for wear, both seemingly intact. I returned to Iowa City and received my M.S. in January 1956.

During the few remaining months at Iowa, I looked at four job possibilities: Seton Hall Dental School (it has since ceased to be), Emory University Dental School (it, too, has closed), Maryland Dental College, and the University of Minnesota. I was invited to join the faculty of all four schools. A somewhat bizarre incident occurred during my interview at Emory. The dean told me, "You'll be our token Jew, Gorlin." "No, sir," I answered, "I'll be your token ex-candidate," and left. I readily accepted Minnesota's offer of $8,800 and was appointed in February 1956 as associate professor and chairman of the Division of Oral Pathology.

The move to Minnesota took place as our second child, Jed, was to be born. Our first, Cathy, had been born at

the Naval hospital in Great Lakes at a charge of $2.75. Our second, delivered at Harkness Pavillion in New York, cost several hundred times that amount.

### Oral Pathology and Minnesota—the Early Years

When it was taught at all, oral pathology in the 1940s usually consisted of a few lectures delivered by a member of an oral surgery department or someone from what was then called the "oral diagnosis" area. Oral pathology first began to take on the formal trappings of a discipline in the late 1940s. About half a dozen pioneers formed the American Academy of Oral Pathology in 1946 and the American Board of Oral Pathology in 1950. What was considered to be adequate training in the early years was remarkably variable. Much of it was literally dental pathology rather than the oral manifestations of systemic disease. Individuals who came out of a background of general surgical pathology such as the Armed Forces Institute of Pathology had a distinct advantage.

I had the great good fortune to have had a predecessor at Minnesota, Dr. David Mitchell, who had come out of oral diagnosis but who had a Ph.D. in pathology from the University of Rochester. Hence, the transition to autonomy for the field at Minnesota was made easier by his earlier efforts.

I am often asked whether I had difficulties as a dentist trying to storm an historically medical bastion. The answer is a resounding no! I can think of but a single incident which occurred during my early days at Minnesota. A well-entrenched surgical pathologist at the University who ran an outside biopsy service heard that I was planning to contact the dentists of Minnesota to apprise them of the availability of an oral pathology biopsy service. I learned that he had written a bill to be presented to the legislature that prevented anyone other than a physician from reading a pathologic slide. After initial apprehension, I sought counsel from my friends at Mayo Clinic, Malcolm Dockerty, Ed Soule, and Dave Dahlin. They saw to it that the bill never came out of committee. I never asked how.

I feel strongly that I accomplished more because I was *not* a physician as I never threatened anyone's turf—and that nearly always involves economic wherewithal.

I find it somewhat ironic that dentists, especially young ones, know me for an unusual cyst that I first described in 1962 but had expanded on over the years, hence the name, the Gorlin cyst. It is an entity which all dental students are required to remember for oral pathology quizzes and dental board exams. In fact, it is not unusual to be introduced to dental colleagues as "This is the cyst!" [85, 110, 372].

My arrival at Minnesota was definitely not the big bang. Realizing that something should be done to alert the dental profession to oral pathology, we initiated a plan to conduct a Mass Oral Cancer Clinic. This had never been done before and, under the auspices of the American Cancer Society of Minnesota, a small cadre of us carried it out. It may not have been the blind leading the blind, but it was certainly the halt leading the halt. We knew essentially nothing about doing surveys, and even less about organizing a small town. We decided to devote several hours of education and training to the dentists and physicians of Willmar, Minnesota (population ca. 5,000), teaching them how to examine facial skin and oral cavity for malignant and premalignant lesions. We enlisted business associations, church groups, granges, newspapers, radio stations, and dozens of social groups to propagandize for us. We cadged gallons of sterilizing solutions, myriad examining instruments, two dozen hospital screens, and the use of an armory to carry out the "laboratory exercise." We limited the screenees to those over 35 years of age, but had no idea whether anyone would appear. In actuality, over 1,000 people came from over 100 miles away for their "free oral cancer exam." The model we established after carrying out 17 such clinics was copied for mass breast cancer examinations in the 1960s [36, 68, 130].

Soon after I arrived I met several veterinary pathologists who brought me slides of oral lesions from various domesticated and, at times, feral animals. Combining my intense interest in the pathology of odontogenic tumors in humans, I extended my work to animals, visiting the pathology laboratories in all the veterinary schools in the United States and Canada. The chiefs of those departments generously let me study the related material from their files. This resulted in several publications [12, 14, 15, 16, 25, 40, 43, 67, 76, 103, 119, 129, 132, 150, 169, 175, 191, 197, 204, 209, 211, 249].

### Syndromes, Syndromes, and More Syndromes

When students ask me how I ever came to such a strange field as syndromes, I never hesitate to tell them my story of pure serendipity. It was simply a matter of hearing the right lecture at the right time.

As I recall it, Columbia Presbyterian was not a hot bed of liberalism during the 1940s. While they were represented in the basic sciences, the clinical areas of medicine were not heavily populated by Jews and Italians. In fact, I'm not sure I knew any. Helen Ollendorf Curth was a very qualified dermatologist. She had come to New York to escape the Holocaust. She was the daughter of two world famous dermatologists from Vienna. But that apparently cut no ice with Columbia's Dermatology Department. She received no appointment. An invitation was issued to her by a part-time dermatopathologist to give a lecture in his course on her favorite disease, acanthosis nigricans. We now know that acanthosis nigricans represents a nonspecific keratinocyte proliferation secondary, inter alia, to a deficiency of insulin-binding receptors. This causes a comparative increase in circulatory insulin which, because of its similarity to insulin like growth factors, binds to keratinocytes and stimulates them to proliferate, a reaction seen in many disorders. However, in the late 1940s, we were only in the clinically descriptive stage of many conditions. Based upon her experience, Helen divided acanthosis nigricans into an autosomal dominant benign form, a pseudoacanthosis nigricans seen in rather obese brunettes, a nongenetic so-called malignant acanthosis nigricans, and a miscellaneous group that included various associated endocrinopathies and Crouzon disease.

I was transfixed, listening to her expand on what she called the malignant form. By that term, Helen meant the occurrence of hyperplastic skin on the neck, lips, tongue, flexural sites, inframammary area, umbilicus, axillae, groin, palms, etc. of patients with "gastric adenocarcinoma." Skin lesions were pigmented and studded with acrochordon-like excrescences, mucosal lesions were not. The concept that there could be cutaneous and mucosal signs of internal malignancy was something I had never encountered before—and I was captured.

After the talk, I approached Helen and asked her what these associations were called. "Syndromes," she answered in her delightful Viennese accent. "*Syn'* means 'together' and *'drome, drome, drome'*—, I forget. Why don't you look that up!" I found a medical dictionary and returned a minute or two later. "Run, run together," I offered.

"You could do me a great favor and tell me about other syndromes that affect the face and mouth as I am a dentist."

"Good Lord, a dentist, what are you doing in a course in dermatopathology?" I went on to explain how I was trying to expose myself to areas of learning that would help bolster my belief that oral pathology should be less dental pathology and more oral manifestations of systemic disease.

My thoughts regarding any role I might play in defining oral syndromes percolated for several years. It was not until I had been at Minnesota for a year or two that I began what was to be a professional lifelong association with pediatrics and dermatology which gave me the opportunity to see syndrome patients with oral changes. I called these *stomadromes*, a term which fortunately never caught on. I remember spotting a patient in 1958 with Gardner syndrome and after searching the literature found an earlier reference to the disorder by a dentist named Fitzgerald. The name I gave at that time to the condition, Fitzgerald–Gardner syndrome, pleased no one. Requiescat in pace!

Another vivid memory that still brings a smile to my face involved an extremely popular TV puppet show, *Kukla, Fran and Ollie.* Kukla was a clown, Ollie a one-toothed dragon. The program, a creation of Burr Tillstrom, was devoured nightly by my children. After seeing several young patients with a single maxillary central incisor, short stature, and isolated growth hormone deficiency, I playfully suggested the name Ollie syndrome. My cohorts, Liz Rappaport and Bob Ulstrom, both pediatric endocrinologists, chuckled. Fortunately before Liz submitted the paper to the *Journal of Pediatrics* under that name, I tracked down Mr. Tillstrom to get his permission. His letter was charming. It read: "I do not think it wise to name your disorder the Ollie syndrome for the following reasons: (1) you state your patients were dysmorphic. Ollie, on the contrary, is quite eumorphically handsome—as dragons go, and (2) his single upper incisor is prehensile. I will virtually guarantee that none of your patients has that ability, and finally (3) and this is most important, if you do, I will sue your ass off"—signed, Burr Tillstrom. The term I used facetiously to satirize my own ofttimes mode of naming syndromes, "monosuperocentroincisivodontic dwarfism," was never meant as a serious contribution, but has actually been copied by other authors.

The so-called "Gorlin sign" also was an oddment of syndrome history of dubious value. I love children and to calm the fears of small patients often "make like Donald Duck" or simulate a trombone with my lips. The patients, often in their turn, do something odd or perform a strange moué. It is not uncommon for me to encourage children to show me what they do to impress other kids on the playground. It was just such occasions that caused me to observe that children with Ehler–Danlos syndrome type I could touch their nose with their tongue tip. In fact, one patient could insert his tongue into his nostril. I then began to ask a series of such patients to do this and found that at least half of them could. At one of the March of Dimes Birth Defects meetings I casually announced this, as an aside, and Victor McKusick illustrated it in one of this texts labeling it "the Gorlin sign." This bizarre discovery led me to investigate the whole subject of "lingual calisthenics," a subject about which I am often appropriately razzed. I suspect that the ability to do all sorts of lingual tricks is under oligogenic control and that the "Gorlin sign" is simply more common in those with unusual collagen. For example, Scott Bloom, the 6-year-old brilliant adopted son of the smartest genetic counselor I know, has osteogenesis imperfecta. He discovered that he could do this trick and, being impressed that several of his friends with OI share that talent, is currently doing a small survey. All that at 6 years of age. Clinical geneticists, look to your laurels!

Priority is always sticky stuff. If one searches hard enough, one can usually find a paper secreted in an old German or French journal that reported a syndrome long before one was born. But be that as it may, the following is a list of syndromes or genetic disorders that my colleagues and I at least helped to define or for which we have often been given undeserved credit: nevoid basal cell carcinoma syndrome (Gorlin–Goltz syndrome) [60, 90, 91, 120, 208, 229, 248, 420, 422]; Gorlin–Chaudhry–Moss syndrome [65, 417]; oral facial digital syndrome, type I [71, 74, 77, 189]; focal dermal hypoplasia (Goltz–Gorlin syndrome) [86, 99, 242]; oculo–auriculo–vertebral dysplasia [96]; Bart type epidermolysis bullosa [136]; unknown Hurler-like syndrome [143]; oto-palato-digital syndrome type I [144, 151, 205, 251, 282, 297]; multiple mucosal neuroma syndrome [163, 240]; sensorineural hearing loss and congenital heterochromia iridum [174]; frontometaphyseal dysplasia (Gorlin–Cohen syndrome) [176, 356, 377]; hypertelorism, microtia, and facial clefting syndrome [181,186]; LEOPARD syndrome [183, 231, 245, 376]; frontonasal dysplasia [199, 226]; X-linked variety of Robin sequence with congenital heart anomalies [203]; cleft palate, stapes fixation, and oligodontia [230]; skin test for MEN 2b [232]; Y body in hair root sheaths of males and in prenatal sex determination [238–240]; Cowden syndrome [254, 289]; oligodontia, taurodontia and sparse hair growth [262, 298]; megepiphyseal dwarfism [283]; W syndrome [293]; microtia, absent patellae, and micrognathia [300, 472]; leukonychia totalis, multiple sebaceous cysts and renal calculi [304, 307]; alopecia totalis, nail dysplasia, and amelogenesis imperfecta

[306]; focal palmoplantar and marginal gingival hyperkeratosis [315]; single maxillary central incisor and solitary growth hormone deficiency [316, 332, 454]; dyssegmental dwarfism-Handmaker type [336, 347]; autosomal dominant osteosclerosis [340]; Usher syndrome, type III [351]; profound sensorineural deafness and oligodontia [353]; AR agenesis of permanent dentition [357]; AD cemental dysplasia [384]; oto-palato-digital syndrome, type II [393]; GAPO syndrome [398]; fibrochondrogenesis [399]; autosomal dominant holoprosencephaly [402]; Melnick–Needles syndrome in males [421]; urofacial syndrome [423]; ermine phenotype [435]; SHORT syndrome [442]; canine radiculomegaly and congenital cataracts [455, 470]; pseudotrisomy 13 [458, 467]; Noonanoid multiple giant cell lesion syndrome [460]; double dens invaginatus of molarized maxillary central incisors, premolarization of maxillary lateral incisors, first deciduous molars, and sensorineural hearing loss [471]; Thai mesomelic dysplasia [478]; X-linked isolated oligodontia [482]; oropharyngeal desmoid fibromatosis, congenital glaucoma, cataracts, and calvarial defect [473].

Of course, many other of our publications addressed new aspects of already recognized syndromes, but I will spare the reader and myself the onus of having to cite them all.

Students, especially graduate students, assume that because I have written 500 articles, chapters, and books that it "was easy for me."

In truth, writing has never come easy to me. Brilliant sentences never issue from my pen. I work, and rework and work a sentence once again. I have always envied the individual who puts pen to paper but once and produces a flawless product. One would think that something could be learned from 45 years of scribbling, but for me it was as painful writing the 500th paper as it was to prepare my first in 1948.

I would be remiss were I not to reveal that I always have what I term *postpartum blues*; i.e., I feel unduly depressed for several months after a book is published. My wife chides me and insists that it is really "empty nest syndrome."

Many times have I said "I have no more books in me" and then find myself writing still another. The need to collect, analyze, reconstruct, and make sense of the many threads of a syndrome seems to generate the energy to start still another, to share what I believe I know and/or see so clearly. I keep expecting the well to dry up—yet so far the bucket still contains a few drops.

### Nevoid Basal Cell Carcinoma Syndrome

In large part, it was chance that determined that I volunteered to help a friend who wished to go on vacation in January 1958, two years after I came to Minnesota. I promised to sit in his Minneapolis dental office on Saturdays and take care of "emergencies." As in most cases, no real emergencies presented themselves—but I received a phone call from a woman who wanted me to "X-ray her jaws for those pesky cysts." After several minutes of inquiry, I determined that she had 20–30 cysts removed from both jaws dating from the age of 7 years. This unusual story greatly roused my curiosity since I could not imagine what type of cysts they might be. The patient told me that she was 39, that she had several cysts removed at the University of Minnesota School of Dentistry, and that her dentist in the "early days" had been Dr. Daniel Ziskin, my mentor at Columbia University Dental School during my fellowship days.

Following our phone conversation, I called my oral pathology laboratory and found that one of my graduate students, Dr. Nat Rowe, was working on his M.S. thesis and, therefore, was there on Saturday afternoon. After telling his story, Nat repaired to the laboratory, found myriad slides of myriad jaw cysts removed from my patient, examined them, and told me that they "looked boringly uniform." He added that the epithelium seemed to pull away from the underlying connective tissue. That description didn't help me much at the time but he was correct, they were odontogenic keratocysts.

I arranged to see the patient the following Saturday morning. In came a middle-aged woman with macrocephaly, distinct kyphosis, and several small lesions scattered about her face that looked to me like basal cell carcinomas. She wore a prosthetic left eye due to "some congenital defect." As she predicted, there were several new jaw cysts present.

I suggested that my patient have biopsy of one or more of these skin lesions and that perhaps this could be done by my colleague, Dr. Robert Goltz, a rising star in our dermatology department.

After discussing the matter with her cousin, a well-known figure from Chicago in mucopolysaccharide research, she acquiesced. In the interim, puzzled by her disorder, I garnered records and radiographs from several hospitals where she had been treated for various problems over the years. I noted that she had calcification of the falx cerebri, several bifid and splayed ribs, and pelvic calcification evident on a flat plate of the abdomen.

Searching the literature on combinations of jaw cysts, rib anomalies, and basal cell carcinomas, I came up almost empty handed, but in a then recently published AFIP fascicle on skin tumors I found a picture of a woman who I suspected had the same disorder as my patient. The woman was stated to have had an affected child. This information, suggesting dominant inheritance, caused me to search the literature once more for inherited basal cell carcinomas. The yield wasn't much better. Our patient was unmarried and was not likely to change her status. Her family had no stigmata of the syndrome. I suspect it was out of frustration that Jorge Yunis and I karyotyped my patient, not suspecting that we would find anything but were astonished to discover an "uncoiler chromosome 1," as it was then called, an unrelated polymorphism that on subsequent investigation ran through her family in an autosomal dominant manner [91].

After amassing as much data as we could and with further literature search back to 1880, Bob Goltz and I wrote "Multiple Nevoid Basal Cell Epitheliomata, Jaw Cysts, Bifid Rib-A Syndrome," which was published in *New England Journal of Medicine* 262:908–911, 1960. If there was any effect from that paper, it was mostly on

me. The little ripples it caused were in the form of letters from various dermatologists "who had seen similar cases and in their patients they found . . . ," etc. It was in this way that I met Jim Howell, M.D., of Dallas, Texas, who contributed greatly to our understanding of the disorder.

Cases of the syndrome continued to accumulate and in 1963, 1965, 1970, 1971, 1972, and 1987, my co-authors and I periodically reviewed the disorder. In the 32 years since our first paper, several patients with the syndrome stand out in my memory. One young fellow who worked in a pet store in St. Paul was bitten by a cobra that was temporarily housed there. He was rushed to the city hospital on a motorbike that crashed into a truck on the way to the emergency ward and suffered a fractured neck of his femur. While recovering from both afflictions, it was noted that he had several basal cell carcinomas scattered over his face and I was brought in on consultation.

Another involved a phone call one January from a sheriff in Montana who wished to know whether having the disorder causes "mental aberrancy," as he put it. It seems that a 16-year-old female had been told that because of bilateral ovarian fibromas (a not uncommon finding in the syndrome) she would be sterile. She became depressed and having imbibed much too much whiskey to drown her sorrow, took a header out the nearest window. Fortunately, the window was no more than six feet off the ground and she landed unhurt in a snowbank. The sheriff took her to the station to sober up and she was claiming that he "manhandled" her. Hence, the sheriff's question. I told him that, in my experience, in spite of the ovarian fibromas, sterility is not a problem and that this good news should cheer her up considerably.

Beginning five years ago, about five or six times a year I would receive a request for blood for DNA studies for gene localization of the syndrome. A rather substantial body of correspondence between me and several investigators ensued. In August 1991, I received a note from Dr. Alan Bale of Yale inviting me to a small get-together of people who were interested in "Gorlin syndrome" at the 8th International Congress of Human Genetics in Washington, D.C. I attended with many of the individuals who were pursuing the gene locus. The meeting reminded me somewhat of C.P. Snow's *The Masters*. It was soon obvious that sharing positive information was not to be, and that even sharing negative information was unlikely but at least feasible. Within a few months, the discovery that the gene was at 9q31 was simultaneously made by Peter Farndon et al. of Birmingham, André Reis et al. of Berlin, and Alan Bale et al. of New Haven. Alan also showed that the syndrome results from the uncovering of a tumor suppressor gene at this site, which explains not only the inordinate number of basal cell carcinomas but the cardiac fibromas, fetal rhabdomyomas, medulloblastomas, ovarian fibromas, lymphomesenteric cysts, odontogenic keratocysts, etc.

I should like to digress for a few moments to restate my firm belief that no work is done in a vacuum. Although this disorder has been named Gorlin syndrome, perhaps because I have had such a sustained interest in it, a veritable horde of investigators have contributed to its understanding. Other names have been employed, such as nevoid basal cell carcinoma syndrome. But it is misleading since only about 50% of white patients 20 years of age or older manifest significant numbers of skin cancers and only a rare one becomes aggressive. In blacks, the skin cancers often do not ever present. The term basal cell nevus is not acceptable as the lesions are basal cell carcinoma from the very beginning. I am personally opposed to eponyms since they say nothing about the disorder, frequently give rise to argument regarding priority of discovery, and may be chauvinistic and unfair to those whose contributions to knowledge of the syndrome far exceed those of the individual for whom the disorder is named. Perhaps, at some distant time a nifty system for an International Nomenclature of Syndromes will be devised and universally accepted, but I doubt it.

### Books, Chapters, and Co-Authors

It was somewhat of a shock to realize that I have also written 60 chapters [19, 20, 69, 78, 79, 83, 105, 121, 146, 147, 160, 161, 165, 208, 209, 211, 212, 214–219, 246, 248, 255, 258, 278, 320, 323–326, 330, 337, 339, 343, 348, 349, 355, 358–362, 364, 375, 387, 400, 419, 420, 434, 436, 440, 446, 452, 462, 469, 480, 483] and have co-authored or edited 20 books [107, 220–222, 250, 279, 280, 291, 317, 318, 328, 329, 354, 363, 390, 429, 430, 439, 444, 456, 457, 464, 465], some of which had Russian and Spanish translations.

This seems especially strange, as I am not a facile writer. In human genetic circles, my best known text, *Syndromes of the Head and Neck*, was originally published in 1964 with Jens Pindborg, undoubtedly the world's best known and revered oral pathologist. The second edition was published in 1976 with Mike Cohen added. In 1987, Mike and I asked Steve Levin to join us. The text was totally rewritten and greatly expanded. It was published in 1990. Although the title did not reflect the coverage, we decided to let it stand.

It was my good fortune to meet Richard Goodman when he was a Genetics Fellow with Victor McKusick in the early 1970s. I had delivered several talks at Johns Hopkins and had met him during one of those trips, just as I had met Judy Hall and Charlie Scott. There was immediate rapport and Rich and I co-authored *An Atlas of the Face in Genetic Disease* and *The Malformed Infant and Child*. Both had second editions. Another happy union was joined with Bruce Konigsmark. Bruce was a neuropathologist at Johns Hopkins who became interested in genetic deafness, largely through his association with Victor. I met him on several occasions and he asked me to participate in a joint venture which resulted in *Genetic and Metabolic Deafness*, published in 1976. Mike and I asked Helga Toriello to share the writing and editing of a new version, *Hereditary Hearing Loss and Its Syndromes*, to be published in 1994.

My best known effort in oral pathology was a graduate or reference text that we called *Thoma's Oral Pathology*. Kurt Thoma was a Swiss-born oral pathologist who had written a monumental multieditioned tome in the 1930s. Although Dr. Thoma had long retired, my co-

author, Henry Goldman, a pioneer oral pathologist from Boston, and I so named our text to honor Dr. Thoma. It was published in 1970. It was a great sorrow for me when the second edition, almost completed, never saw the light of day. Several dusty chapters still grace my shelves, often providing me with useful references for rare facial or dental anomalies.

If I had even a touch of the metaphysical about me, I would do my best to discourage individuals from co-authoring any text with me as Bruce Konigsmark, Richard Goodman, and Steve Levin died untimely deaths. Bruce and Steve had chronic myelogenous leukemia and neither saw the fruits of their labor. Richard and I had talked about doing a magnum opus or encyclopedia on congenital malformations. It is with great satisfaction that it will see the light of day under the aegis of Roger Stevenson and Judy Hall in early 1993 and will be a wonderful memorial to his vision.

## Disappointments and Regrets

I view it as a personal failure that I was not able to produce more M. Michael Cohens. Perhaps 30 or 40 graduate students went through our program in oral pathology and while most assumed careers in that regimen, it was really only Mike that was infected by my zeal for dysmorphology. I like to explain this away by saying that in dentistry, one couldn't make a living trying to diagnose unusual individuals. But Mike did it, like I, by combining his catholic interests with conventional oral pathology duties. Perhaps, it was the times that allowed us to do this. It probably could not be readily accomplished now. Requirements originally elastic, become solidified, almost calcified, as fields mature. It was also good economic times for dental schools, when oral pathology divisions were several people deep, allowing us to "do our own thing." With severe fiscal constrictions, activities such as dysmorphology would be considered nonessential fluff. I suspect that I was the first and Mike was the last in line.

Most of the dentists who had an interest in human genetics have died, retired, are soon to be retired, or have switched their interests to other fields of endeavor. They are not being replaced. The field shall not soon again see another Carl Witkop, a veritable giant in so many areas, inter alia pigment disorders, oral cytopathology, and genetic disorders of the teeth. The number of young dental investigators who are being trained in molecular biology and genetics is miniscule. Human genetics, as a requirement, is taught in few dental curricula. Considering the economic plight of dental schools, there will probably be far fewer in number in a decade and no great likelihood that human genetics will be part of any of their required programs.

## Academia and Professional Societies

Academic advancement progressed with my appointment as Professor of Oral Pathology in 1958, the youngest full professor at the University. Four joint appointments followed as I was named Professor in the Departments of Laboratory Medicine and Pathology, Department of Pediatrics, and the Department of Dermatology in 1971 and the Departments of Obstetrics and Gynecology and Otolaryngology in 1973.

The American Academy of Oral Pathology played a large role in my early career. I became a member in 1950, served twice as vice-president (1957–1958; 1964–1965), as secretary-treasurer (1958–1964), and as president (1966–1967). I played a similar function in the International Society of Craniofacial Biology, being elected President in 1969–1970. For the American Board of Oral Pathology, I served as Secretary-Treasurer from 1970–1974, Vice President from 1974–1975, and President 1975–1976.

I joined the American Society of Human Genetics in 1960 and served on the Board of Directors from 1982–1985.

My writings in oral pathology, especially on odontogenic tumors, resulted in my serving on the World Health Organization Center for Histologic Nomenclature and Classification of Odontogenic Tumors and Allied Lesions from 1966–1980. I played a similar role for the National Institutes of Health from 1967–1978.

One of the great joys in my life was to serve on the National Foundation March of Dimes Clinical Research Advisory Committee from 1974–1993. The collegiality was incomparable. And for many years (1984–1990) I helped organize the MOD Clinical Genetics Conference. Another pleasure was and is to serve on editorial boards of professional journals which tallied 33 at last count.

## Honors, Mostly Undeserved

It seems strange that 15 years have elapsed since I was selected to be a Regents' Professor at the University of Minnesota, one of then 15 of 1,500 professors to be so chosen. Presumably, this title is bestowed on those of us who were deemed to be the most creative. While I could readily see why several of my confreres had been so selected, perhaps because I least understood their fields, I never really accepted the notion that I was *that* creative. Describing new disorders always seemed so very easy to me that I have felt somewhat guilty wearing the crown. But, be that as it may, it has been a great honor to be so judged by one's peers. The only disadvantage is receiving an occasional letter from someone who is irate about some incendiary issue, mistaking me for a Regent and wanting me to right this specific wrong.

The first honors I received were the Fulbright and Guggenheim Fellowships, which afforded me the opportunity to go to Copenhagen and to co-author with Jens Pindborg the first edition of *Syndromes of the Head and Neck*. In retrospect, it probably was not the best place to write the text as the restrictive biomedical library rules (closed stacks, only three journals per 15 minutes) slowed production considerably.

Washington University chose me as Outstanding Alumnus in 1974. I remember sharing the podium with Buckminster Fuller, a riveting experience for me. A large number of organizations and universities have bestowed on me named lectureships, visiting professorships, and awards. I will not burden the reader by listing them.

An honorary Doctor of Science was bestowed by the University of Athens in May 1982. I remember well the

pomp of the occasion. The award coincided with the 3rd International Clinical Genetics Seminar organized by Chris Bartsocas and as I delivered the opening words in Greek followed by a discussion in English on facial folklore, I was especially honored by having many genetic friends in the audience. John Opitz sat in the front row.

Certainly the most flattering experience one can have is being selected by the American Society of Human Genetics to help create the American Board of Medical Genetics. It was a humbling learning experience, partly from the realization that it is difficult to write unambiguous questions.

Several relatively recent honors have befallen me: Honorary Fellow-Royal College of Surgeons of Ireland, Dublin (1984), Honorary Fellow-Royal College of Surgeons of England, London (1990). These ceremonies were a strange amalgam of solemnity and 24 carat joy. I shared the first honor with David Poswillo, one of England's finest oral and maxillofacial surgeons. The second was given at the same time to Mark Ferguson, England's most famous experimental embryologist.

In 1989, I was most flattered to be included within the august group (Joseph Warkany, F. Clarke Fraser, Hans Zellweger, John Opitz) who received the Col. Harland Sanders Lifetime ("Chicken-Licken") Award for work in birth defects from the March of Dimes. And in the same year, I received the Robert J. Gorlin Chair in Dysmorphology. This allowed me to initiate an annual meeting to effect a union between clinicians and basic scientists in the field of molecular embryology. During 1990, I received the Burroughs Wellcome Visiting Professor Award by the Royal Society of Medicine, London. The panoply was awesome.

## Hobbies and Interests

Perhaps because my early education was so shaky, after being exposed to humanities and history at Columbia College, I began to read extensively in those areas as well as mythology and folklore. While I was living in a small town in New Jersey, I was first introduced to the concept of the evil eye (malocchio) by boyfriends of Sicilian origin. The notion that one could have one's life affected by another's jealous glance intrigued me, and while I never bought into the notion, I was impressed by how many of my childhood acquaintances did. As opportunities became available, I read books devoted to the subject, attended conferences, and corresponded extensively with folklorists and cultural anthropologists regarding amulets and talismans to counteract the influence (influenza). I probably now have one of the larger collections of 35-mm color slides for my talk on the subject.

Many hours have been devoted to collecting pictures of a multitude of Habsburg family members from many world museums and private collections. The idea that an oligogenic condition such as the characteristic mandibular prognathism and maxillary hypoplasia could simulate a dominant disorder due to consanguineous unions in each generation captured my interest, and I have often delivered art history talks on this subjects interweaving gobs of Habsburg family gossip.

As a dentist, I could not ignore the artistic and utilitarian subject of ivory or dentin. Its use since 35,000 B.C. as an art form has held my interest for at least two decades and I periodically give illustrated lectures on ivory artifacts made from over half a dozen animals.

Other subjects that have stilettoed me are the history of syphilis, messianic cults, bias, i.e., how people make decisions, and strange artifactual disorders.

## Confreres

Mike Cohen, first as student, then as peer, now as teacher, was always and will be a paragon of what one would wish for to carry on and to extend one's effort in new directions. I have indeed been blessed. Mike not only far surpassed any conceived goal I had envisioned for him but made craniosynostosis and its syndromes his own bastion, his own bailiwick. My fervent wish is that Mike will have the great good fortune, in his turn, to find his own Mike and initiate him or her on a career in dysmorphology.

Perhaps Len Langer, a pediatric radiologist nonpareil, has forgotten some details of a case he reviewed in 1975, but I see no evidence of any erosion of his Betz cells. He has the mind of a bear trap. Our association has been pure delight for me. He has taught me so much about radiographic subtleties.

One cannot discount in any way the everyday aid and sustenance given by one's co-workers. Bob Vickers, Heddie Sedano, Jarda Červenka, and Carl Witkop by their efforts afforded me the time to "do my own thing." I despised administrative duties, neglected them as often as I could, avoided faculty meetings as if they were the source of bubonic plague, and consequently was no good at that job. Specifically, I believed in selecting individuals and letting them decide what they could best do. Bob Vickers, the peerless oral pathologist, was not only the master behind the microscope, but a great organizer and businessman. I never had hesitation in turning over the reins to him. Heddie Sedano, a fine oral pathologist with a genetics bent, whom I met in Argentina, joined me in 1962. He bore the teaching load like a stalwart and became our computer maven. Jarda Červenka, from Prague, whom I had the good luck to encounter in 1965, and who spent two years (1965–1967) with me, returned home, only to flee to the West in 1968 when the Russians invaded. Jarda established the first cytogenetics clinic in a dental school and was responsible for the training of the present director and codirector of the Cytogenetics Division of Laboratory Medicine and Pathology, University of Minnesota.

Carl Witkop is one of the most unique individuals to grace the halls of dentistry. He was not only a superb oral pathologist and geneticist but an authority on pigment disorders, his recent focus being a monumental study of the Hermansky–Pudlak syndrome. Carl taught me much about oral cytology in myriad disorders, and none was his peer in hereditary disorders of the teeth. He is the last of the breed.

## Family

I suspect that each of us thinks that one's family is special and I am no exception. I have accomplished my work surrounded by love and support, probably failing

to do things I should have done. However, our family of 40 years has been a very stable one in which mutual respect has been the hallmark. I have tried not to force my views or expectations on my wife or children, hoping rather that laissez-faire affords greater development.

My wife, Marilyn, has always been inordinately supportive in my many endeavors, has buoyed me during my postpartum blues, has shared in bringing up two wonderful children, and has tolerated my many foibles for these four decades.

Our firstborn, Cathy, is head of family law at a law firm in Minneapolis and we delight in the opportunity to share time with her two children. Our son, Jed, is a pediatrician hematologist-oncologist and molecular geneticist who is second in command in the blood bank at Boston Children's Hospital. We manage to see our other grandchild three or four times a year.

### Illusion and Reality

Rarely does a week go by that I am not asked by a student or colleague, "What do you plan to do in your retirement?" or even "Now that you're retired, how do you spend all your time?" It is indeed a strange feeling to realize that one is or at least looks as if one were in the December of one's career. I hasten to assure them that I'm not retired, in spite of my impending 70th birthday—that I have been saved from having to perpetually tend my garden (which in Minnesota is not easy to do from October to May) by the gracious financial support of Dr. Guilan Norouzi, a former student, who helps me perpetuate the illusion that I'm still productive, that I still have original thoughts, and that bells still go off when I envision a new syndrome.

I am still midstream in our text, "Hereditary Hearing Loss and Its Syndromes," which will be published in a year or two by Oxford University Press, to be a companion piece to the 3rd (1990) edition of "Syndromes of the Head and Neck."

Dr. Norouzi and my wonderful secretary, Carol Church, apparently still see a spark of creativity in these old embers and to them I am endlessly grateful in so many ways, more than I can articulate. I believe that "The web of our life is of a mingled yarn, good and ill together." But life has been kind to me and, yes, very generous. I am most fortunate in still having the respect of my confreres. It is my profound hope that I recognize when I am no longer contributing and have the good grace to check out without a whimper.

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