



Children with **Wide Smiles**

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I still remember very vividly that late summer afternoon many years ago at the clinic in the University Hospital in Prague, when I saw for the first time a real baby with a bilateral cleft lip and palate. There was no comparison with all of the pictures I remembered from my medical books! His mother was holding him and he smiled at me with his whole face: with his beautiful eyes, chubby cheeks, and—with a very wide smile. His upper lip was twice broken by clefts. He was of the same age as my baby boy Martin. Comparing these two baby faces hurt more than I should have allowed as a professional.

Many times I recall that moment. I was just a fresh pediatrician looking forward to my medical career to cure and to help heal physical and emotional pain. But at that time I felt hopeless, because I knew that even repairing his cleft would not completely solve his problem.

I believe this experience and endless questions—"Why did this happen?," "What did I do wrong?," "Is this going to happen again to me, to my children..?," etc.—that mothers of cleft children asked me motivated my professional orientation toward understanding causes of facial clefts and finding ways to prevent them.



Cleft Facts

Cleft lip and palate anomalies are the second most common birth defects and the most common and the most serious anomalies of the craniofacial region. The disfigurement involved leads to serious psychological, adaptation, and physical difficulties for affected children and their families. Treatment is challenging, expensive, and lengthy. Including individuals with an orofacial cleft which is a part of a syndrome, one child with a cleft is born among each 560 newborns. Translated into time, a baby with a cleft is born somewhere in this world every two minutes, 660 per day, and 235,000 per year. In the U. S. 7,500 babies with a cleft are born every year.

In the developed countries (including the U. S.), treatment of individuals affected with an orofacial cleft is well developed and the vast majority of babies born with clefts have a good chance to go through life with similar opportunities, chances, and goals as others. The number of specialists involved and the number of years of treatment result in a high cost. A conservative estimate of an average lifetime medical cost for one individual with cleft lip/palate in the United States is about \$101,000. This includes an immediate cost of \$30,000 in the first year of life alone. This year alone the medical cost for babies born with orofacial cleft in the United States will total \$750 million. As surgeries are covered by insurance, there is no child with an unoperated cleft in our country. However, the orthodontic treatment, an essential part of a successful outcome, is, unfortunately, not sufficiently covered in many cases and therefore we are still seeing quite a few individuals who were born with cleft having less than perfect final results.

However, a different story is found when a child with an orofacial cleft is born in an undeveloped or developing country. There, cleft lip and palate anomalies represent a life-threatening defect for newborns and infants because cleft of the lip and palate makes breastfeeding impossible (cleft of the lip prohibits a seal of the baby's mouth around the breast nipple, and cleft of the palate prohibits a formation of a necessary negative pressure in the oral cavity; both are indispensable for suction). In many families of low social economical class, breast milk is the only source of food for a cleft child. In addition, feeding presents a serious risk of aspiration due to an open communication between the nasal and oral cavities. Therefore, a baby is at risk of malnutrition and of a delay in consecutive growth and development. The risk of infections and other health problems is also increased. When a baby survives it does not have access to needed corrective treatment in many cases. Children and adults with disfigurement of the face are excluded from society because of unintelligible speech and a stigma that cannot be hidden.

Approximately 25 % of children born with a cleft in developing and undeveloped countries will never have even a surgical repair of a cleft lip. Therefore, about 150 non-governmental organizations (NGOs) have organized surgical missions for more than 40 years to provide free reconstructive surgeries to underserved individuals affected by orofacial clefts. Although a vast majority of those helped this way are children, it is not rare to see a man or woman over 60 years old with an unoperated cleft seeking a surgery from the mission.

Even if a number of these missions is increasing, it seems obvious that they cannot solve this serious health problem.

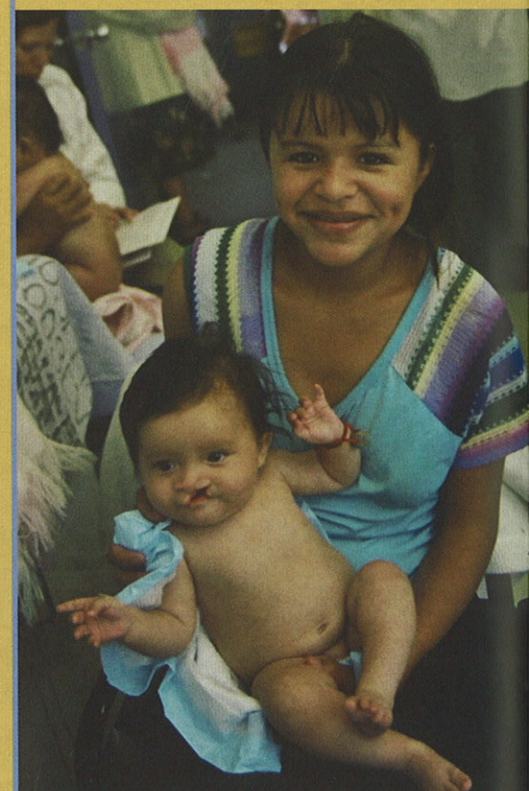
What Can We Expect?

With a projected natural increase of births of 1.8 million/year, we can expect an additional 3,200 new cases per each year. This increase is occurring primarily in the low social class groups. A generation from now, the number of cleft individuals living on this planet will increase from six million to eight million.

Each individual affected with orofacial cleft has in average 12 unaffected relatives who are at high risk of having an offspring affected with cleft (10-40 times higher risk than the general population). Because clefts have a significant genetic component, both individuals affected with a cleft and their non-affected relatives are at a statistically significant higher risk to have a child with a cleft compared to the general population. The genetic factors creating susceptibility for CLP are passed to more relatives in populations with large families (having a higher number of children). This is occurring in the poorest and fastest growing segments of the world.



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Is There a Solution?

Yes. The solution is to invest in prevention and at the same time improve treatment and make it more generally available. There is no better professional field than dentistry to demonstrate that investment in prevention is the investment with the highest return. It is not surprising that the vast majority of research projects to identify causes of orofacial clefts is being conducted in dental schools and dental institutions around the world.

We can proudly count Pacific School of Dentistry among those working on the solution. We are among only a few focused on the major clinical application of this research on prevention.

It is understood that cleft lip and palate anomalies are caused by the interaction of genetic and environmental factors. It seems to be generally understood that the major environmental factors lie in nutrition and diet. We are not able to change our genes, however, we can learn which genes and their mutations form "genetic susceptibility." We may be able to change the diet, nutritional patterns, and lifestyle habits of those at greatest risk.

Pacific Goes Into the Field

We can be extremely proud that Pacific is making a significant contribution in this effort. Since 2001 faculty and residents in the Department of Orthodontics and our undergraduate students have been actively involved in medical missions organized by Rotaplast International, Inc. Rotaplast (www.rotaplast.org) is one of many NGOs providing free reconstructive surgeries for underserved children affected with cleft and craniofacial anomalies. This organization was founded in 1992 by Dr. Angelo Capozzi, a plastic surgeon and past president of California Plastic Surgery Association, and Peter Lagarias, Esq., at that time President of the San Francisco Rotary Club, and has since sponsored more than 4,000 surgeries. Moreover, Rotaplast is among the first of such organizations to introduce a multidisciplinary team approach to the surgical missions. It is definitely the first one to include genetic research aimed at prevention of orofacial clefts.

Missions are widely supported by Rotary Clubs worldwide. My first Rotaplast mission in 1997 in Tunuyan, Argentina, inspired me to become a Rotarian myself. I have had the privilege of serving as the director of genetic research and prevention of the Rotaplast, and I have had an opportunity to participate in 26 missions to Latin America and Asia.

Since autumn 2001 Pacific has participated in 20 Rotaplast medical missions, and donated dental and orthodontic services averaging \$12,000 per mission, altogether \$200,000. Half of these missions involved a genetics research component, which in donated value of professional and diagnostic services represents an additional \$20,000. This means our faculty, orthodontic residents, and dental students contributed the equivalent of almost a half million dollars to the Rotaplast effort.

And behind these numbers are children whose lives were changed—2,000 of them! About 100 children receive free surgery from the Rotaplast team during each mission. Of those patients our team examined, the majority needing care were able to receive it.

Pacific Goes Into the Lab

However, participation in field missions is just one of the ways Pacific is contributing to the understanding and prevention of orofacial clefts. The field projects also support an active, ongoing research program involving faculty, residents, and students at the schools. Six masters theses for our orthodontic residents are based on such data collected during the field trips. Numerous table clinics by our residents and undergraduate students and several presentations at national and international meetings have been based on these datasets.

For example, at the International Association for Dental Research Meeting in March of 2004, the Pacific Orofacial Cleft Group made four presentations. The presenters included orthodontics resident Cory Costanzo '02 and Hee Soo Oh. Dr. Costanzo presented findings on the significance of a new mutation that is responsible for cleft anomalies in Guatemala and Dr. Oh made an epidemiological comparison between cleft populations in Trelew, Argentina, and Chillan, Chile. Terezia Mosby, a research associate, presented data on associations between nutrition of mothers and we have been able to obtain funding for our research from several

sources in addition to support from the dental school. In addition to the regular support from Rotoplast, we have received grants from the University of Colorado in Denver, the March of Dimes, and the Plastic Surgery Foundation. Strengthening our research team are the expertise and time of adjunct faculty members and collaborators such as Dr. Claudine Torfs (epidemiology), Dr. Miroslav Tolar (molecular biology), and Terezie Mosby who leads our research efforts on nutritional factors in clefting.

The dental school has been able to equip a molecular genetics lab using funding from grants. We have been able to initiate molecular genetic research in the craniofacial field which is comparable to other dental schools and are generating research findings that are competitive internationally.



Here are some examples of our research results: Environmental and dietary factors seem to contribute more than MTHFR mutations to the high prevalence of clefts in Cumana, Venezuela. Mutations of candidate genes associated with metabolism of folate are present in a significantly higher prevalence among cleft populations compared to the general population. Thus, very probably, they contribute greatly to the etiology of orofacial clefting in Guatemala. The composition of the diet in families of cleft children contributes to dental problems of children affected with cleft during the mixed dentition stage. Seasonal prevalence of cleft anomalies in Barquisimeto, Venezuela, seems to be influenced by rainy season. The highest prevalence of children born with orofacial cleft is correlated with conceptions that occurred during the rainy season months. Very probably, pesticides, fertilizers and other chemicals infiltrated into the drinking water during the rainy season. Based on results above, we have extrapolated that mutations of "candidate" genes that we have studied which form genetic susceptibility for cleft lip and palate, as well as environmental factors triggering clefting, are very likely "location specific." Further, nutrition always plays an important role among environmental factors.

Conclusion

We are building the foundation for becoming a major cleft prevention and treatment center that will serve Northern California with dental services for those who are affected with orofacial cleft.

All of us at the Pacific School of Dentistry who have participated in a mission have added to our unforgettable memories: the little faces of these children, their smiles and tears, and also the grateful faces of the mothers holding their babies after surgeries. All of us realize that there are many people who are far less fortunate than we are, and that we have the responsibility to share a little bit of our wealth and our time with them, and it is our professional obligation to use our skills not only when convenient financially but also when our help is needed. □



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