The Challenge and Opportunity in Craniofacial Anomalies

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There is an increasing awareness that the research community does not function in the isolation of an ivory tower but is dependent upon the social, political and economic climate of the time. With the increased demand for health care, rising costs, and the contraction of federal spending in the health sciences, new priorities for research are being identified which command an increasingly larger segment of the diminishing supply of research funds. The current emphasis is on the delivery of health services, medical aid for the disadvantaged, and the training of more health personnel (*23*). Unquestionably, these social forces will shape the future of health science research as much as the conceptual and methodological discoveries that may emerge from our laboratories and clinics.

It is against this background of ferment in our institutions, and drawing from my own experience as director of a multidisciplinary organization concerned with craniofacial anomalies, that I pose two interrelated questions: Why study birth defects? Do such studies belong in the curriculum?

As one administrator put the issue to me: "What you are doing is interesting and may even be worthy of support by the National Institutes of Health, but it is not relevant to the current thrust in medical education or to the concern for delivery of health services to patients. Our students just aren't interested in what you are doing. They will see few of the kinds of patients that concern you. If they should encounter such a patient, you can be sure that they will quickly refer him to a regional medical center. What you teach isn't worth their time."

More recently, one of my colleagues was interrupted in the midst of a lecture on the genetic transmission of disease by a self-styled militant radical who protested what he labelled as "a lecture on freaks" and demanded that more time be spent on the social problems of the disadvantaged.

Lest you think that my story ends in despair at this point, let me reassure you that the administration and an increasing number of faculty and students have urged our greater involvement in the development of

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the curriculum. They recognize that the Center for Craniofacial Anomalies at the University of Illinois is not an isolated enclave devoted to esoteric pursuits but a unique model for the delivery of comprehensive and exemplary service to patients who are often poorly managed in the traditional departmentalized clinical structure of the hospital.

The multidisciplinary center is a classroom for the extended education of the specialist who then brings back to his departmental teaching a broader view of patient needs thereby minimizing the universal complaint about the narrowly oriented specialist. For the student, the center demonstrates a concern for the patient's problems in the context of his family, school and community. The uniqueness of the patient population and the specially trained professional personnel required provide the basis for regionalization of such services within a university medical center operating in linkage with governmental and welfare agencies, satellite units, and community health resources on a metropolitan and multi-state basis.

What are the arguments in favor of the establishment and support of such centers in the light of current national priorities? What justification is there for assigning students to clinics that care for relatively rare clinical entities?

Why Study Birth Defects?

It should be recognized that congenital malformations, morphologic and metabolic, are being studied with increasing interest by an ever widening array of disciplines whose interests range from molecular and cell biology to population genetics and epidemiology. This concentration of interest represents more than the current fashion in science. It stems from a universal recognition of the relatedness of such problems to the public health and the fundamental import to basic science of the knowledge that can be gained from these studies.

In this connection, the National Institute for Dental Research is to be commended for its foresight and early support for research and training in this field. This involvement was heralded on a large scale with the sponsorship of an international symposium in 1959 (*19*). To place that event in historical perspective, I would note that it preceded by one year the First International Conference on Congenital Malformations organized by the National Foundation and by two years, the first formal meeting of the Teratology Society.

In 1959, at the Gatlinburg symposium, I offered the following reasons to justify the importance of birth defects as a public health problem (*19*).

> 1. The profile of pediatric practice has been changing. Among the advantaged nations, ten times as many children die as a result of congenital malformation as of five contagious diseases once greatly feared. This change is a relative change characterized on the one hand by reduced morbidity due to infection, and on the other by increased recognition of a greater variety of congenital morphologic and metabolic anomalies.
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> 2. Clinical interest in birth defects have been made more respectable by

decreasing emphasis on the "bad egg" concept which stigmatized families and inhibited open discussion in the public press. Newer knowledge regarding the interaction of genetic and environmental factors coupled with an increased social maturity made it respectable to discuss these matters openly and changed our attitudes. The candor of President Kennedy's family in publicizing mental retardation as it affected one of their own is a case in point.

3. There was a concern then, as now, regarding the genetic effects of man-made radiation that polluted the atmosphere. Please remember that 1959 was the B.T. era in teratology—that is, before thalidomide. The tragedy made us terribly conscious of environmental factors and their effect on the ecology of the fetus. It was not until 1962, in the aftermath of thalidomide, that an ad hoc Commission on Drug Safety was funded by the Pharmaceutical Manufacturers Association (*22*).

With mounting concern over the increased pollution of the environment from a variety of sources, and the inevitable effect on the quality and quantity of life, we have come to recognize that developing organisms, man and animal alike, are being affected by a wide variety of drugs and chemical agents. It has been pointed out that the effect of thalidomide was discovered relatively quickly because it produced a rare and striking malformation which just couldn't be missed. Suppose, however, that thalidomide had caused club foot, polydactylism, or even cleft lip and palate, how long would it have taken to discover the increased incidence and to trace the effect to the drug? For these reasons, there is a pressing need for the application of computer techniques to the processing, analysis, and dissemination of a wide variety of data that may relate incidence of malformation, in man and animal, to changes in the environment.

Consider the use of anti-convulsant drugs in the treatment of epilepsy. Such drugs are administered to many women in the child-bearing period. There is increasing suspicion that there is an association between the intake of such drugs and the birth of children with facial clefts. Yet, to my knowledge, no one has organized a wide scale collaborative study to monitor the teratogenic effect of the anti-convulsant drugs.

Symbiosis of Research and Education

Apart from these obvious needs for continued and further investigation, research has another function which is not sufficiently stressed by educators nor interpreted to legislators who appropriate funds to support higher institutions of learning. I am referring to the fact that research is basic to the educational process by which we train clinicians. Research serves by validating what we think we already know and in producing new knowledge and new techniques which form the substance of what we teach our students and what we do for our patients. It is my fear that in the haste to train more health service personnel, the collateral responsibility for the development of a new knowledge through research may be diminished.

As a clinical investigator and teacher, I am reminded that Harvey Cushing pointed out that every patient poses two questions for his doctor.

First, what can I learn from the patient? Secondly, what can I do for the patient? At first glance, the priorities posed by Cushing seem contrary to the humanistic ideals of medicine. On reflection, however, it becomes clear that in order to treat a patient on a rational basis, understanding of the individual must take precedence.

To understand what we can learn from the patient, let us define the patient with a craniofacial birth defect in terms of our therapeutic goals. Dr. Edward F. Lis, Director of the Division of Services for Crippled Children of the University of Illinois, stated that this patient presents an intertwined medical, dental, emotional, social, educational and vocational problem requiring prolonged supervision for optimal habilitation (*19*).

If you accept this definition, then it is obvious that shuttling such patients through the maze of departmentalized hospital clinics, or by referral to an assembly line of isolated, specialized private practitioners, can not provide the necessary integrated services. This scheme does not provide the comprehensive care that the birth-defect child requires. What is needed is a specially trained generalist who is responsible for review of all aspects of the child's function within his family, school, and community (*8*). Since few health scientists are trained to function in the interdisciplinary milieu required for such patients, it became necessary to establish a new kind of training program.

For the past 21 years, we have gained considerable experience in the organization and management of an interdisciplinary center. I can report that our trainees were tutored in comprehensive patient care, family medicine, the total ecological setting of the patient and the delivery of health services utilizing regional and community resources long before these became the *"in-phrases"* of our current jargon.

What I am suggesting is that the diagnostic, treatment, research and educational forum that we developed for the care of birth defects provided a microcosm for the study of a variety of needs basic to all patients. It is these same values that seem to have been rediscovered of late.

The problem and the mission to which our center was dedicated demanded utilization and application of a wide array of conceptual information and methodologies that challenged the trainee in a manner that had not been done before.

It compelled the medical student, for example, to relate to disciplines that he might not ordinarily encounter during the course of routine training. In the process, he found common cause with the behavioral scientist, the speech pathologist and the dental specialist. Everything the trainee had ever learned in his pre-clinical sciences found application in the effort required to unravel the etiopathogenesis of birth defects. What mattered most, and this became evident to the trainee as well as his mentor, was that the knowledge gained in the specialized setting increased his insights and added to his capability in dealing with the more common clinical problems.

As an example, consider the training of a pediatrician. Admittedly, he needs to know about speech and language development, and growth of jaws and development of dentition. It is to the pediatrician that the anxious mother will first address her concern about such problems. Unfortunately, such information is seldom dispensed in the course of pediatric training. Assignment to a craniofacial birth defects clinic provides frequent and vivid display of organ-function interrelationships in speech physiology. The immediate availability of dental and speech science personnel to discuss these problems serves to instruct the pediatrician. The principles derived from this instruction transcend in their application beyond the problem that provoked the discussion. Thus, problem-oriented teaching augments the curriculum by motivating interest in basic principles and demonstrating their immediate application to the solution of a clinical problem. In the process, the student's perspectives are enlarged to an extent that the conventional didactic presentation can seldom accomplish.

Does the study of congenital malformations belong in the curriculum of the undergraduate?

There is a history of concern for the "experiments of nature" which permeates the literature of biology and medicine. McQuarrie (*11*), a pediatrician, observed that the experiments which nature makes upon our fellow creatures are often unique in that they cannot be duplicated in the laboratory or reproduced at will in the clinic. Such experiments of nature, properly considered, permit acquisition of new and useful knowledge applicable far beyond the patients and anomalies studied. Advances may be anticipated from the study of these experiments that concern organ, tissue or cellular function, physiologic interrelationships and the nature of pathologic processes.

McKusick (*10*), in his introduction to Gorlin and Pindborg's book, *Syndromes of the Head and Neck,* echoed the geneticist Bateson who said "Treasure your exceptions!" He went on to quote the eloquent appeal that William Harvey wrote in 1657 on the usefulness of the study of rare diseases.

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.

Smith (*26*), in the introduction to his book, *Recognizable Patterns of Human Malformation,* invoked a similar quotation from James Paget, Lancet, 2: 1017, 1882.

> We ought not to set aside with idle thoughts or idle words about "curiosities" or "chances". Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question—Why is it rare? or being rare, why did it in this instance happen?

In a collection of essays dedicated to the thesis that some kind of fundamental advance in science can be made only from study of disease, Paul Weiss (*28*) wrote about deformities as cues to understanding development of form. Weiss, the experimental biologist, echoed the words of McQuarrie, the clinician, in drawing attention to the extraordinary insights and the suggestions for laboratory investigation that can be gained through the study of "experiments of nature" in man. We are reminded in this connection that the clinical observations by Gregg led to the discovery of the teratogenic effect of the rubella virus.

Garn (*7*), in a foreword to a book on human growth, noted the investigative advantages inherent in the study of the abnormal. "Differences and interrelationships, barely discernible even at the fifth or ninety-fifth percentiles of normal growth become more clearly delineated.... Growth retardations hold potential for the understanding of normal growth when the cause of the retardation is known and so one term in the set of simultaneous equations."

I can expand on Garn's thesis by adding that, given a wide enough spectrum of congenital malformations, one can develop an array of natural experiments that would define many terms in the set of equations and in a way that would be impossible to duplicate in the laboratory.

It should be clear from the foregoing that for a long time scientists from many disciplines have recognized the value of studying abnormalities, particularly of man, our most intimate acquaintance. Statistical evidence also indicates that at least in the developed countries, congenital malformations rank as a major cause of infant mortality and morbidity. What remains to be demonstrated is how this opportunity to study man should be organized and what results can emerge from such investigation. Therefore, for the remainder of my time, I want to discuss the history of the organization I represent and list some of its accomplishments.

Like all new ideas thrust into a traditional and conservative environment, an interdisciplinary center for the sole purpose of serving children with cleft lip and palate was at first ignored, viewed with suspicion, or regarded with downright hostility. That such interdisciplinary units survived at all testifies to the utility of their mission and the merit of hybrid vigor in human organization as in plants.

We began with a categorical mission to develop a Cleft Palate Center and Training Program. It was recognized at the outset that a longitudinal growth study was basic to our understanding of facial clefts; that we should begin with the infant prior to the intervention of treatment, and that it would be advantageous for all specialists to see things from their

beginnings through various stages of postnatal development. Our growth data at the outset consisted solely of cephalometric radiographs, casts and photos.

Looking back to the beginning of that program, I am glad that we did not have to submit a research application such as is required by the National Institutes of Health. I suspect that the purposes, specific aims and methods stated at the outset would have had little relation to what followed. There was no foretelling that the casts and cephalometric radiographs would ultimately revise our thinking about the epidemiology of clefts and add insight into the development and genetics of facial clefts.

It did not take long before the accumulated data on unoperated clefts taught us what was wrong with much of the research that preceded, including a great deal that was current. To borrow an analogy from Feinstein's excellent book on clinical investigation (*6*), it can be said that investigators wrote about cleft lip and palate as though it were a single homogeneous fruit salad, rather than a mixture of homogeneous fruits.

As a result of our experience, the first task was to describe the spectrum of variation encountered and develop a meaningful taxonomy. In fact, the first published sentence to emerge from our research read, "Not all clefts are alike"(*16*).

There is another by-product of this research that has not been sufficiently advertised. Plastic surgeons have no way of learning the pathologic anatomy of clefts except in the operating room. There are no specimens avialable in the dissecting or pathological laboratories for the study of clefts as there would be for the study of congenital heart deformities.

Although plaster casts of infants' faces and jaws and cephalometric radiographs may be a poor substitute, they offer the only means by which to instruct the surgeon-in-training on the variable anatomy he will encounter prior to surgery. In addition, the library of data collected over the past twenty-one years provide the surgeon with a clear understanding of the natural history of post-natal development and the response to various surgical technics. Until such longitudinal data were accumulated for study, the surgeon possessed no means for the visualization, let alone analysis, of the various types of clefts.

Meskin (*12*) working with this material, was able to challenge the validity of birth certificate data in the epidemiologic assessment of facial clefts. These same data led to the hypothesis of sex differences in palatal development (*13*), which stimulated others to confirm this theory by direct observation on human embryos (*4*).

Most of the investigations that related to our longitudinal data can be categorized as prospective, retrospective and laterospective. Prospective studies include descriptions of the postnatal changes in craniofacial form as a consequence of growth processes or as the result of specific therapeutic intervention. As a result of serial studies, three general patterns of postnatal growth have been demonstrated. In the Pierre Robin syndrome,

most cases demonstrate substantial improvement through catch-up in growth of the mandible. In mandibulofacial dysostosis, the pattern of growth is such that the deformity observed in infancy or early childhood is maintained throughout the growth period. The deformity of the mandible neither improves nor worsens in the course of time. The third pattern is one in which the growth process is so deranged that the severity of the deformity increased with age. This has been observed in some instances of unilateral agenesis of the mandibular ramus, in the malignant form of osteopetrosis, and in the growth of the maxilla and neurocranium in some forms of premature craniofacial synostosis (*18*).

Specific clinical entities, such as the complete bilateral cleft lip and palate, have been singled out for intensive study by means of metallic implants, according to the method of Bjork (*3*), and histologic examination of the premaxillary-vomerine suture. As a result of these multifaceted studies, we have been able to demonstrate overgrowth in the premaxillary-vomerine suture as a contributory factor to the midface deformity that characterizes this cleft type.

Retrospective investigations have been motivated by psychosocial and speech evaluations. To account for variable success in the habilitative effort, the records of early childhood are being examined for somatic factors and symptomatic experience that could explain current developmental status. Patients with the Pierre Robin syndrome provide an excellent model for this type of study. The severity and duration of the stress experienced in infancy in a large series of such cases can be placed in rank order and related to the developmental status determined in later years.

Laterospective studies are designed to search for other malformations that may be associated with facial clefts in sufficient frequency and pattern to provide some clue as to common causality (*14*). As a result of this approach, we have demonstrated a relatively high prevalence of certain types of congenital heart defects (*25*) and discovered a high frequency of irregular electrocardiographic findings in the absence of other pathology in patients with facial clefts (*9*).

Roentgencephalometry has aided in the elucidation of the nature of the craniofacial malformation associated with facial clefts as it affects the mandible (*17*), maxilla (*1*), orbits (*2*), nasopharyngeal area (*5*), and the base of the skull and cervical vertebrae (*15*). Current studies on the variable growth and involution of tonsils and adenoids have raised a number of questions of interest to immunologists.

There is mounting evidence that the shape of the mandible may be syndrome-specific for Pierre Robin, Cornelia de Lange, mandibulofacial dysostosis, cleidocranial dysostosis, and pycnodysostosis. Such specificity may assist in delineating syndromes with overlapping characteristics and provide genetic markers useful in family studies (*20*).

Since children with certain types of facial clefts have a higher frequency of associated malformations, it was inevitable that we would

become involved in the management of additional craniofacial malformations which came within our purview. This included patients with premature synostosis of the craniofacial sutures, otocephalic and oculocephalic syndromes.

The child with microtia, malformation of the temporal bone, maxilla and mandible, as well as various soft tissues, has not received the attention focused on facial clefts. The complexity of the intertwined problems in this syndrome, and its incidence, warrant the same kind of team effort as is directed toward facial clefts. Our first step was to record all of the findings derived from the x-ray, including temporal bone tomography, audiometry, and otology, in a form suitable for electronic data processing. This provided a means for interrelating the severity of findings in contiguous organs, thus expanding our insights into the nature of the regional developmental defect and establishing a rational basis for treatment (*21*).

This cursory review provides a representative sample of what can be accomplished with sufficient case flow, meaningful longitudinal data, and a professional staff with pluralistic interests. As a result of our interdisciplinary training program, we have created a new professional hybrid, the craniofacial biologist. He may be an ophthalmologist who wants to understand how abnormal growth of the midface may affect the architecture of the bony orbits and visual function, or he may ask how abnormal development of the eye may influence growth of the upper face. In the same setting, the dental specialist realizes that the temporomandibular joint does not end at the fossa but entails an appreciation of the temporal bone as well. Interaction between disciplines became possible by the creation of an operational and educational structure designed to solve problems which were refractory to solution by traditional methods.

What of the future and particularly, a future in which the prospects for increased federal funding of research projects and centers is not promising? The recently published directory of facilities providing services for children with cleft lip and palate (*24*) is a serious indictment of the delivery of health care in our country. There are too many centers, often within a single metropolitan area, that operate on a part-time basis with inadequate staff, and insufficient case flow.

There is an urgent need to consolidate such clinics, establish regional university-affiliated centers that can organize consortia which make use of various facilities in the region. It is crucial that duplication of equipment and personnel be avoided while striving to provide optimal service for the greatest number of patients at the lowest possible cost.

Let me cite one example in which collaboration between institutions can increase productivity and minimize costs. Computerization of cephalometric data is an absolute essential at this time if we are to make effective use of our accumulated data. To trace and measure by old fashioned techniques is to hobble our mission and waste human and material resources.

At the beginning of the 1960's, a few workers began to look to computerized methods to transcribe roentgencephalometric data electronically and develop machine-methods for the storage, analysis and computation of data previously done by hand by senior investigators as well as graduate students. As methodology improved and hardware became available, it was evident that expensive "professional coolie" labor was not only wasteful but inadequate to cope with the task of analyzing multiple bits of information from each of hundreds of cephalometric films.

Our group is at a critical stage of beginning to convert all of our information-handling operations to a computer base. Recognizing that two groups at the University of Michigan had succeeded in developing some of the technologies essential to our needs, we sought to benefit from their experience.

Since Dr. Geoffrey Walker of the Dental Research Institute at the University of Michigan had progressed in developing programs and normative data complementary to our own, we were able to work out collaborative projects that were of benefit to both our groups. Most important of all, the job is being done at minimal cost to both of our institutions.

It is clear that priorities will need to be established to guide the expenditure of the shrinking research dollar. This shrinkage results not only from cutbacks in federal appropriations but also is attributed to the increased number of scientists competing for funds, inflation of costs, and the identification of additional problems worthy of support.

How should money be spent on congenital malformations? Since an ounce of prevention is worth a pound of cure, it is obvious that the emphasis should be on prevention. However, can we be sure that the answers will be found by an approach at the molecular and cellular level? Warkany (*27*), in his summary statement to the Third International Conference on Congenital Malformations, cautioned that these approaches, however brilliant, must not be the only ones for the key to prevention may be found at the level of clinical observation as well.

My concluding remarks are addressed to the bright young graduate in dentistry who feels overtrained for the practice of clinical dentistry and undertrained to function as a laboratory investigator. To satisfy his intellectual cravings, he may be drawn into graduate study in a basic science only to drift away from where he is sorely needed in clinical investigation. The opportunity and the challenge in congenital malformations is such that everything he has ever studied, in the basic or clinical sciences, becomes relevant and important. What greater fulfillment can we hope for in a chosen profession?

Epilogue

In submitting this paper to the Cleft Palate Journal, it seemed appropriate to rethink the message as it applies to the future of the American Cleft Palate Association. Those who have witnessed the transformation of

the organization from the American Academy of Cleft Palate Prosthesis to its present form are aware of the change in its constituency and the quality of its meetings. The Association, if it is to continue to prosper, must be sensitive and responsive to the changes that affect its mission and the needs of its membership, both active and potential. The appointment of an ad hoc Committee for Exploration of Changing Interests of the Association augurs well for its desire to respond.

My concern is that the Committee may not be bold enough in its recommendations for change. One fundamental change is the need to revise the articles of constitution to abolish the rotation of the "troika" of disciplines that guide the association. The time is long overdue for the association to become pediatrically oriented. To paraphrase Gellis (*8*), the pediatrician has by default, given over to plastic surgeons, speech and hearing specialists, psychologists, social service workers and dentists, the care of children with craniofacial birth defects. It is not necessary that he regain control of these areas, but he must become sufficiently informed and skilled to serve as a generalist or ombundsman for the handicapped child and his family. This scheme does not depreciate the role of other disciplines but recasts them as part of an invaluable ancillary team.

The association has failed to take the initiative in dealing with other birth defects that demand the same resources that have been mobilized to deal with facial clefts. The status of care for children with otocephalic syndromes, craniofacial synostoses, and of adults who have undergone ablative surgery is similar to that which prevailed for facial clefts a generation ago. The challenge and the opportunity is for the Association to expand its horizons to include additional but related clinical problems.

Summary

In 1949, the Cleft Palate Center and Training Program was established at the University of Illinois Medical Center by a grant in aid from the Children's Bureau then a part of the Federal Security Agency in the period preceding the establishment of a Department of Health, Education and Welfare. Since that time, this multidisciplinary unit has evolved into a Center for Craniofacial Anomalies. The perspectives derived from this experience may be pertinent to the long term goals of the American Cleft Palate Association and are relevant to the current thrust in education for the health sciences and the delivery of health care in the United States.

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