Congenital Malformations: Clinic and Experiment*

JOSEF WARKANY, M.D.

The American Cleft Palate Association has long expressed interest and appreciation for etiologic research. It speaks for an association dedicated to rehabilitation of those born with handicaps and disadvantages that it finds time to pause and to take stock in its activities. There are many among you who see the immediate clinical problems as well as the wider implications of your specialties. It is generally admitted that progress has been remarkable in alleviation of the fate of children born with craniofacial abnormalities, defects of particular gravity since they spoil the first impressions made by a human being, his face, his smile, his tone of voice and speech. Correction of the child's facial handicaps is of outstanding importance because it facilitates integration into family, school and society. It is understandable and justified that those who contribute to these corrective measures are proud of their achievements.

As one who is not directly involved in rehabilitation of these handicapped children, I may be allowed expression of a different view, a view derived from experiences and observations of a different specialty, an approach called pediatrics. To the pediatrician treatment, care, repair and rehabilitation are *necessities* but prevention is his aim. To express such a remote objective in regard to craniofacial malformations may seem unrealistic and pretentious but for the pediatrician it is a reasonable target.

From its beginning pediatrics has been a specialty directed at prevention. Dealing with children we look at patients differently from those who treat adults and diseases which come with age and decline. Most children are born healthy and disease seems like an avoidable interference by adverse environmental conditions. The bulk of diseases encountered by the founders of pediatrics were infectious and nutritional. The leaders in pediatrics early recognized that treatments were palliative but seldom curative and from the beginning of the specialty they sought *prevention.* To wipe out the contagious diseases, to prevent rickets, enteritis and other forms of malnutrition seemed an unattainable dream, a pious wish and idle talk. But it has happened within a lifetime. The nutritional and contagious diseases that we were trained to treat, diseases that filled our hospitals to overflow, and diseases that killed thousands of our patients

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Dr. Warkany is professor of Research Pediatrics at the University of Cincinnati and Fellow of the Children's Hospital Research Foundation, Cincinnati, Ohio.

have been reduced to rarities. In fact, the knowledge in care and treatment of these patients is of little value today and the pediatricians of a generation ago have worked themselves out of their jobs. Consequently, huge sums that would be spent daily for patient care and treatment are saved daily; unfortunately, these savings go unnoticed and unappreciated by a younger generation. Of course, this unbelievable success was not achieved by pediatricians alone. Many branches of science and technology have contributed to the accomplishment but pediatrics had prepared the way by outlining and classifying the diseases, by showing the limitations of treatment, by critical evaluation of the panaceas recommended and by favoring prevention.

As the most obvious and devastating diseases subsided, it became clear that there was a substantial residue that had escaped the attention of early pediatricians in their attempts of prophylaxis. Congenital malformations were among these remnants for which preventive measures seemed out of the question; they and many other less defined disorders emerged as pediatric problems that still contribute to children's morbidity and mortality. Children with congenital malformations are now receiving treatment from pediatricians and many other specialists; they receive the benefits of reconstructive surgery and the aids of rehabilitation. But most of us will admit that in spite of excellent results in repair, perfection is seldom achieved. In the treatment of congenital malformations an obstacle is encountered that is rather characteristic of teratologic phenomena: Congenital malformations are often multiple; they affect more than one organ system; they need the attention of more than one specialty. This is the reason why many remarkable partial successes of treatment often fail to produce total success. This habit of congenital malformations to affect an individual in various organs and body systems, this peculiarity of defects to run together in countless combinations and permutations, is the basis of syndromology, an area discussed and emphasized in this symposium. A great deal can be said and argued about syndromes of congenital malformations, their delineations and terminology but their most important message is that treatment of their individual components is not enough and that we must view them as general disturbances which need be investigated as such, with the aim of finding their causes and means to prevent them. Suggestions for such approaches are not lacking.

It has long been recognized that certain congenital malformations run in families and seem to be hereditary but it was not clear why some members were affected while others were spared. These irregularities of transmission became better understandable by rediscovery of the Mendelian laws at the beginning of this century. As these basic principles proved more and more complex and new rules about genetic transmission were established in subsequent decades, it seemed to some that all congenital malformations could be explained on a genetic basis. But the explanations often grew complicated and appeared forced; there was a need for

other interpretations and principles to supplement genetic theories. To the pediatrician who had observed that malformations could develop after birth by inadequate nutrition and other environmental damages—I refer to rickets, tuberculosis, poliomyelitis, etc.—it seemed possible that *prenatal* adverse environmental conditions could also be at the root of congenital malformations. Against this possibility was the belief that the mammalian embryo was so well protected in the maternal uterus that it could not be deformed by exogenous agents. It seemed, therefore, that experimental work was needed to challenge this widespread tenet. Since animal models had been extremely helpful in the elucidation of rickets, scurvy and many contagious diseases it seemed worthwhile to look for comparable animal models for research in congenital malformations. It was of great importance that in 1940 and thereafter it became possible to produce in mammals many types of congenital malformations with various teratogenic methods. The first methods of this kind involved vitamin deficiencies and one of these, riboflavin deficiency, resulted in the production of a syndrome of skeletal malformations which included cleft palate and micrognathia. Since then other methods have become available for production of facial clefts and a considerable literature exists which is concerned with experimental variations of the basic phenomena. It was a step forward to have brought research on congenital malformations into the laboratory and to be able to produce facial clefts at will. But over the satisfaction of ongoing, successful experimentation we must not forget our initial aim which was to create animal models for the prevention of human congenital malformations. Have we achieved this goal or are we on the way? Prevention of facial clefts is still far off, but a great deal has been learned by these experiments. One of the first results was that it was shown that withholding of a single foodstuff such as riboflavin from the maternal diet could cause a *syndrome* of congenital malformations that included palate, mandible, ribs and extremities in a systemic though variable pattern. It was shown that the environmental teratogenic method had variable "penetrance and expressivity" like an abnormal gene. The demonstration that congenital malformations can be produced by adverse maternal environmental conditions altered teratologic concepts and aided in the quick acceptance of Gregg's conclusion that congenital cataracts and heart disease can be the result of maternal rubella. Twenty years later, the experiments had prepared the way for the rapid recognition of thalidomide as the cause of limb defects which had appeared in epidemic form in Germany and in many other countries. This may be the time to point out that animal experiments can also be misinterpreted. Thus the implication that human congenital malformations including facial clefts are due to faulty maternal diets was not born out by subsequent studies. Interpretation of animal experiments requires caution, patience and wisdom.

There are also animal models available for the study of genetic mecha-

nisms leading to congenital malformations. For those interested in facial clefts there are inbred strains which show a heritable tendency to these anomalies; but this tendency is expressed in rather irregular and variable incidences suggesting a complex etiology. These strains were used to demonstrate that an external teratogen, cortisone, can combine with labile genetic constitutions to bring about cleft palate with regularity. This and similar animal models show us how a combination of genetic and non-genetic factors may be responsible for the origin of facial clefts and other malformations.

The complexity of the etiology of facial clefts is also shown in discordance of some pairs of twins that must be considered identical or monozygotic. Since they are derived from one zygote, they originated with identical genetic potentials; if they differ in phenotype, the difference must be due to non-genetic or environmental factors. But as far as we can see, such twins develop in the same environment, in the same mother, in the same uterus and they are nourished by the same placenta. Thus their discordance in regard to congenital malformations must be attributed to minor differences in their environment, concealed differences that determine that one monozygotic twin is normal while the other is malformed. Such *micro-environmental* damaging factors may, of course, be responsible not only for malformations of twins but also for similar malformations of singletons. It is understandable that it is very difficult to discover such microenvironmental and probably fleeting teratogenic events, particularly many months after their occurrence, when the child is born.

This brings me to a point that is seldom emphasized. All congenital malformations are present when the child is born. The pediatrician is the recipient of a child damaged before he is in charge of the patient, before he has access to the patient and before he can do anything for the child. Yet pediatricians have been most active among clinicians in the search for causes of congenital malformations. I fear there are limits to our abilities to find teratogenic factors; micro-environmental damages during early development are examples of accidents that are completely out of our reach and competence.

Is the obstetrician responsible for these early weeks and early damages? It would be a mistake to blame obstetricians for neglect of the problems of teratogenesis and to assign to them alone the care of the embryo. Often the help of the obstetrician is sought at a time when malformations of the unborn child have long been determined, i.e. after the organogenetic period. In fact, there is a no man's land of medical care during the most important weeks of human development. Fifteen years ago, in a lecture in honor of a meritorious, retired pediatrician, I pointed out that there exists a gap in the early care of the unborn child, that there is a field which is not covered by any specialty and I recommended to the medical students and residents present, this area as a challenge, a challenge "that I would take up if I were young." The witty and sarcastic honored pediatrician

retorted: "I must warn you: Don't take Dr. Warkany's advice, or you will starve." Unfortunately, this warning has still some justification. The embryo has no doctor.

Like numerous other congenital malformations, cleft lip and cleft palate are often neither inherited according to simple Mendelian rules nor attributable to obvious environmental causes. They are said to be multifactorial in origin. Whenever multifactorial etiology of malformations is announced by a disappointed investigator, it spells trouble for the genetic counselor who cannot give concise genetic prognoses; he must resort to empirical risk figures which usually have little meaning to concerned parents. But the genetic counselor's embarrassment should encourage the etiologist and the hopeful preventer. If several causative factors are necessary to bring about a phenomenon such as a malformation, there is hope that one of these factors is manageable and removable and that the phenomenon can be prevented. What these necessary and contributory factors are is anybody's guess. They may be molecular, infrastructural, micro-environmental and not perceivable without sophisticated instruments and sophisticated training; or they may be obvious, recognizable with the naked eye and trite, discernible by anybody with an open mind. The rubella embryopathy was discovered by McAllister Gregg, an ophthalmologist and the thalidomide embryopathy was unmasked by the mother of an affected child. If everyday events are contributory factors, they are not easily recognized; but they can become manifest in rare experiments of nature and constellations when epidemic or endemic accidents reveal their contributory role. In such cases a layman can suspect a causative factor as well as a sophisticated investigator. Whether the conclusions from such observations are right or wrong must be tested by experienced scientists familiar with the disorder, its natural history and its usual epidemiology; otherwise such guesses are indistinguishable from meaningless superstitions.

As long as congenital malformations continue as unsolved medical problems the pediatrician should accept the responsibility for the entire child with congenital malformations. He should direct the care and treatment of the child that must be seen and dealt with by many specialists; he should be the doctor who takes overall charge of the entire case. This is not a thankful job since, as I pointed out, the child's handicaps may be multiple and not correctable in some of the cases. The pediatrician should also remain in the center of teratologic research, stimulating and inspiring his clinical colleagues as well as basic scientists, in the search of causes of congenital malformations and of preventive measures.

In summary: These are the years when the public justly demands that medical and paramedical care be available to all citizens, irrespective of economic and social standing. For decades treatment and care of children with facial clefts had had much attention of many specialists and teams of medical and paramedical workers and rehabilitation has been success-

fully achieved. If I understand it right, this symposium had the purpose to point out that symptomatic treatment and repair are not the only approaches to this problem; that facial clefts are signs and symptoms of more general disorders; that facial clefts are not an etiologic entity; and that prevention of these afflictions must be our final goal. It is curious that in recent years research aiming at prevention has lost some of its luster; the public is not aware of the diseases that are no more and does not appreciate the burdens from which they have been freed. You deal with the failures of our preventive efforts. You should recognize and emphasize that etiologic and prophylactic research must be continued, enhanced and applied to fields which so far have not been tilled sufficiently.