Field studies of congenital malformations revealed deficiencies in reporting, and emphasized the principle that anomalies cannot be treated in studies as a single universe. Epidemiological investigations have to consider each anomaly separately and in relation to others, and to search for multiple causes.

FIELD STUDIES OF SELECTED CONGENITAL MALFORMATIONS OCCURRING IN PENNSYLVANIA

Joan G. Babbott, M.D., M.P.H., and Theodore H. Ingalls, M.D., Sc.D., F.A.P.H.A.

IN 1960 congenital malformations accounted for approximately one-fifth of the deaths under one year of age in Pennsylvania, and are an underlying reason for maternal and child health and crippled children's programs. For some anomalies, such as cleft lip and palate, surgery may correct the basic defect, and medical and orthodontic care may ameliorate the associated problems of feeding, speech and appearance. With still other malformations only modest gains can be achieved—hearing aids for the partially deaf, prostheses for the armless, and care and training of the palsied. And yet for the most part, the blind remain sightless, the spastic stay spastic, and the mentally retarded and the mongoloid continue to be candidates for permanent custodial care.

It is now recognized that advances in the management of all such patients with congenital deformities should be accompanied by expanded efforts to determine etiology. This has been especially important since the relationship of rubella to fetal deformity demonstrated that some malformations are acquired in utero, and thus may be preventable.

The search for etiology may involve a case history investigation of anomalous infants, or the study of a specific malformation by its time, place, and person distribution within a defined population. Prerequisites for either approach are accuracy of diagnosis and completeness of reporting. Six pilot studies along these lines are reported here.

A Study of Six Anomalies Occurring in Philadelphia County

This was an investigation of place of residence of all mothers giving birth to babies with anencephaly, cleft lip and palate, ectromelia, mongolism, spina bifida, and tracheo-esophageal fistula as recorded on birth certificates of babies born in Philadelphia County from October through December, 1959. Philadelphia County comprises the city of Philadelphia, and is divided into ten health districts, which had populations ranging from 123,000 to 289,000 in 1959. The six anomalies were chosen for study because they constitute serious handicapping conditions which are evident at

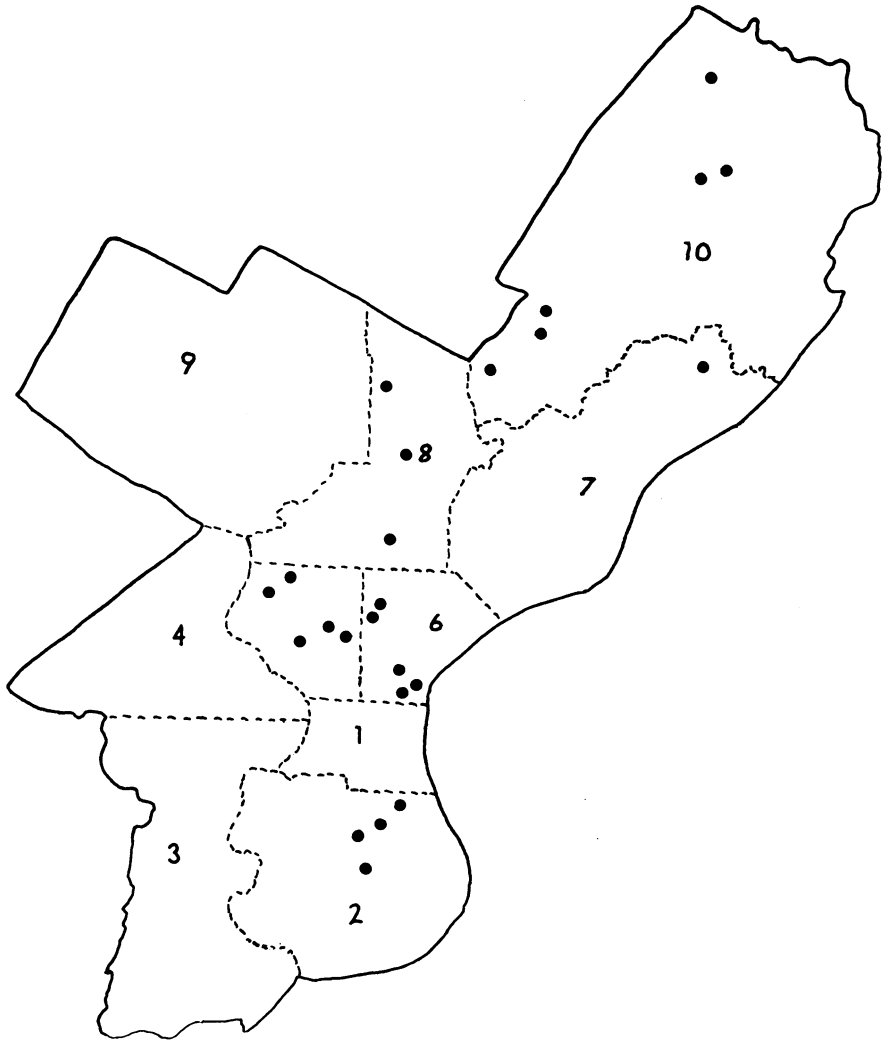

Figure 1—Residence of Mothers of Infants Born with Seven Selected Anomalies, Philadelphia by Health Districts, October-December, 1960

birth, and therefore maximal reporting would be expected.

Initial information on the 24 cases of these selected defects occurring in Philadelphia in the last quarter of 1959 was obtained from birth certificates. In each instance, the mother's physician was contacted, the mother was interviewed at home, and hospital records were reviewed.

The 24 infants, the offspring of 23 mothers, include 11 with cleft lip-cleft palate, four with anencephaly, two with mongolism, two with ectromelia, four with spina bifida, and one with tracheo-esophageal fistula. The fatality rate was high: all of the anencephalic infants and five of the others died; 14 are alive, and the status of one is unknown. These infants not only had major primary defects, but more than half had serious associated anomalies.

Geographic distribution of cases by maternal residence reveals that all but one of these defective infants came from five of Philadelphia's ten health districts (Figure 1). Yet these five districts contributed about the same number of Philadelphia's births, 23,230 births in 1959 as compared with 21,703 births in the other five districts. Nine of the 23 mothers resided in Health Districts 5 and 6, each having a population of approximately 218,000 people. These two districts are well known for their low socioeconomic level and for their high rates of diseases, such as tuberculosis, which are influenced by socioeconomic conditions. However, before a serious search is made to uncover reasons for the seemingly disparate distributions, the accuracy and adequacy of case-finding and reporting practices in different hospitals need to be established. An inquiry of this kind follows.

Birth Certificate Reporting of Congenital Malformations

Except for occasional surveys of hospital births and of pregnant women attending obstetrical clinics, birth certificates are the usually available source for determining frequencies of congenital anomalies. As with other vital statistics, the validity of the information derived from birth certificates depends first upon diagnosis and second upon completeness of reporting. In the field of anomalies, both are unquestionably less than ideal and yet there seems little reason to doubt that a more satisfactory registering of selected defects is attainable. The pilot survey presented here deals with completeness of reporting from two Pennsylvania hospitals. The first was a large metropolitan teaching hospital in Philadelphia, and the second, a good general hospital in a small city of about 100,000 population north of Philadelphia. For the time period July, 1956, through June, 1960, the newborn records of both hospitals were reviewed for the same seven anomalies listed above. All cases found by means of hospital records were then checked by reviewing the birth certificates at the State Office of Vital Statistics.

These data, given in Table 1, revealed

Table 1—Anomalies Reported on Hospital Records and on Birth Certificates, One Urban and One Upstate Hospital, Pennsylvania, July 1955-June 1960

Congenital anomaly	Urban Hospital (12,453 live births)		Upstate Hospital (13,307 live births)	
	Cases Found from Hospital Records	Cases Reported on Birth Certificates	Cases Found from Hospital Records	Cases Reported on Birth Certificates
Spina bifida	9	4	10	8
Anencephaly	4	2	4	3
Tracheo-esophageal fistula	3	1	1	1
Mongolism	12	7	14	8
Cleft lip	6	2	2	1
Cleft lip-cleft palate	2	1	10	10
Cleft palate	3	0	6	6
Total	39	17 (44%)	47	37 (79%)

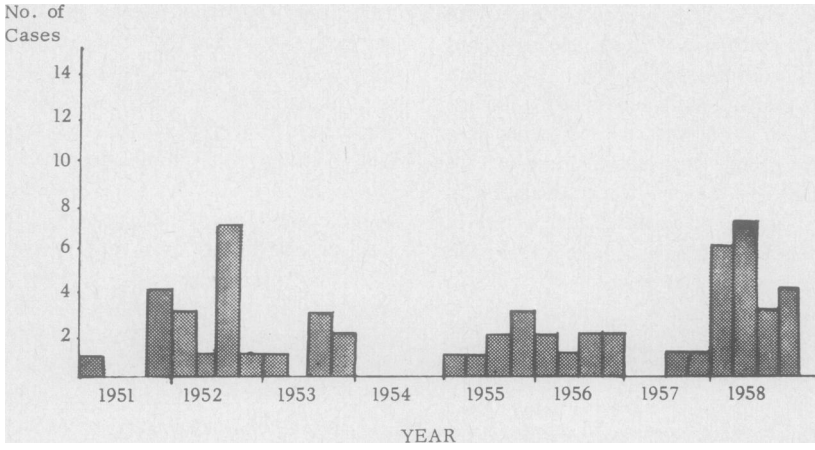

Figure 2—Patients with Tracheo-Esophageal Fistula by Quartile of Birth, Pennsylvania, 1951-1958

that only 63 per cent of these malformed live-born babies were reported as malformed on their birth certificates. The nonteaching hospital reported 79 per cent of cases, whereas the hospital in the urban medical center reported 44 per cent. In addition to a difference in over-all reporting, there were inconsistencies in the completeness with which specific anomalies were registered.

The findings cast grave doubt on the common practice of accepting birth certificate reports of malformations at face value. Further, they demonstrate the necessity for specifying anomalies in order to reach even an approximation of accuracy.

Tracheo-Esophageal Fistula in the Years 1951 Through 1958

A third investigation involving a single, selected defect, namely tracheo-esophageal fistula in Pennsylvania for the period 1951 through 1958, was undertaken because of the relative rarity with which this deformity occurs. It appears in about 1:5,000 to 1:10,000 live births, and any sizable "outbreak" is thus representative of many thousands of births. The distribution of cases in this eight-year period is shown in Figure 2 by month of birth. An over-all rate of about 1 per 10,000 live births was found, which probably represents considerable underreporting of recognized cases. For this particular anomaly, certificates may be filed before definitive diagnosis is made.

A clinical investigation of each case of tracheo-esophageal fistula reported between January and June, 1958, was conducted within 12 months of the births of these defective infants. Thus, recall for major events in the early prenatal period, a critical time for the differentiation of the trachea and esophagus, would expectedly be good. In each instance, the mother was interviewed in her own home; the physician attending the pregnancy was also seen; and when possible hospital and office records were reviewed. The findings have been reported in some detail elsewhere.[1]

Of the 12 babies with tracheo-esophageal fistula investigated in this way, five were premature by weight, seven died shortly after birth, and associated anomalies were found in five. The mothers of these defective infants revealed a multiplicity of problems—histories of infertility and miscarriage, first

trimester vaginal bleeding and first trimester infections of various kinds, including three cases of influenza in the fall of 1957. The significance of this observation is untested but it may be pertinent that in a British prospective study of 578 cases of maternal rubella in the first trimester of pregnancy there were three instances of tracheo-esophageal fistula.[2]

This initial investigation raises questions and provides no answers. One evident feature of Figure 2 is a clustering of cases, this despite relatively uniform birth rates throughout the period of study. Assuredly, reporting is not complete, but neither is there reason to suspect reporting to vary sufficiently between 1951 and 1958 to account for the clustering of 13 cases in 1952 and 20 cases in 1958 or to account for the hiatus in 1954. Such distributions and an association between tracheo-esophageal fistula and maternal rubella suggest that environmental influences operate in causation. Frequency by geographic location is another refinement worth exploring in the future by technics illustrated in Figure 1 and Table 1.

Cleft Lip and Cleft Palate

The value of rapid recognition and prompt recording of selected congenital defects has been stressed already in this paper. In line with this, a pilot epidemiologic investigation of cleft lip and cleft palate was undertaken at the Henry Phipps Institute in cooperation with the Allentown Cleft Palate Clinic, Allentown, Pa.

The Allentown Cleft Palate Clinic is one of nine in Pennsylvania, and serves seven counties in the northeastern part of the state, treating the majority of cases occurring there. Case studies were carried out by the county public health nurses who were acquainted with the purposes of the investigation and had been briefed on a research questionnaire

Table 2—Findings on 155 CLCP Cases from a Pilot Study, Allentown Cleft Palate Clinic, Allentown, Pa., 1959-1960

	Sex Ratio of Cases		
	Male	Female	Ratio
Cleft lip	18	10	1.80
Cleft lip and cleft palate	56	23	2.00
Cleft palate	13	35	0.37

	Age Distribution of Mothers of CLCP Propositi					
	15-24		25-34		35-46	
Cleft lip	12	43%	12	43%	4	14%
Cleft lip and cleft palate	34	43%	34	43%	11	14%
Cleft palate	12	25%	24	50%	12	25%

	Families with at Least One Case of CLCP Besides the Propositus	
Cleft lip	9	32%
Cleft lip and cleft palate	21	26.5%
Cleft palate	7	14%

	Associated Anomalies	
Cleft lip	2/28	7%
Cleft lip and cleft palate	18/79	23%
Cleft palate	10/48	21%

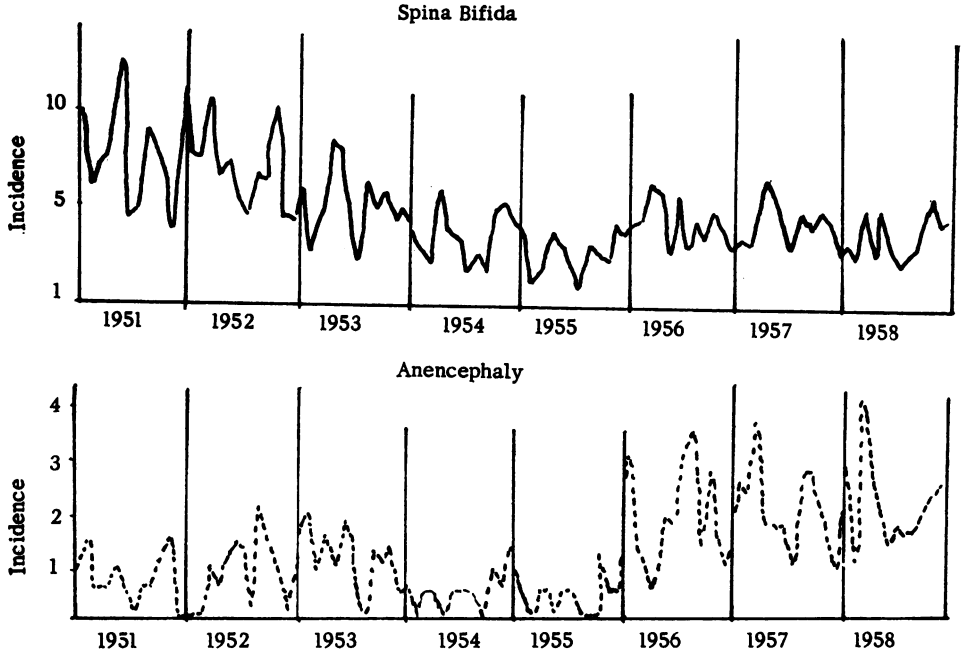

Figure 3—Incidence of Spina Bifida and Anencephaly per 10,000 Live Births, by Month, Pennsylvania, 1951-1958

they were to use. Data were tabulated on 155 cleft lip-cleft palate patients, most of them born since 1950. Some attributes of this series of patients appear in Table 2. Children with cleft lip alone were predominantly male, as were those with cleft lip combined with cleft palate, whereas those with cleft palate alone were predominantly females. Maternal age was lower in cleft lip than in cleft palate. Other attributes pertinent to family history and associated malformations are shown in the table. This line of investigation is still being pursued,[3] one objective being to determine whether cleft lip and cleft palate combined behaves more like cleft lip or cleft palate alone.

Seasonal Distribution of Anencephaly and Spina Bifida

Because European data have suggested a seasonal variation in anencephaly and an increase in anomalies of the central nervous system following maternal influenza,[4,5] a pilot study of anencephaly and spina bifida was initiated, using cases reported on Pennsylvania birth certificates. Specific influenza morbidity figures are not available by month, but it is a matter of common knowledge that the sharp influenza epidemic occurred in the late fall of 1957. Although there is no clear-cut peaking of spina bifida in 1958, it is provocative that the highest rate for anencephaly in the eight-year period studied occurred in March of that year.

A by-product of the study was the demonstration of how risky it can be to equate two anomalies of even the same anatomical system, and postulate that they will show the same epidemiologic characteristics. As Figure 3 indicates, the incidence by month of anencephaly and spina bifida shows no direct or consistent relationship over time. If any-

thing, the frequency of anencephaly seems to have risen between 1951 and 1958, while spina bifida declined, at least from its peak frequency in 1951-1952. As has been pointed out, reporting of anomalies on birth certificates is neither complete nor uniform, but there is no reason to believe that the reporting of anencephaly improved in Pennsylvania between 1951 and 1958 at the expense of spina bifida.

The important lesson to be learned from this pilot study is that an understanding of anomalies can best be made through an intensive investigation of each particular condition. While certain general principles apply to acquired malformations, such as the importance of timing of the infection or stress in pregnancy and factors of severity and dosage, prevention is hastened as we arrive at a clear understanding of specific factors involved in relation to specific kinds of defects. This is how an understanding of the teratogenic role of maternal rubella in causing congenital cataracts and of high concentrations of oxygen in causing retrolental fibroplasia developed.

Racial Distribution of Selected Congenital Malformations

The question of whether true racial differences exist in the incidence of anomalies has yet to be satisfactorily answered. Using birth certificates of infants born in 1960 in Pennsylvania, race data were studied in relation to the following diagnoses: achondroplasia, anencephaly, cleft lip and palate, ectromelia, mongolism, spina bifida, and tracheo-esophageal fistula. There were 452 anomalous babies born to white

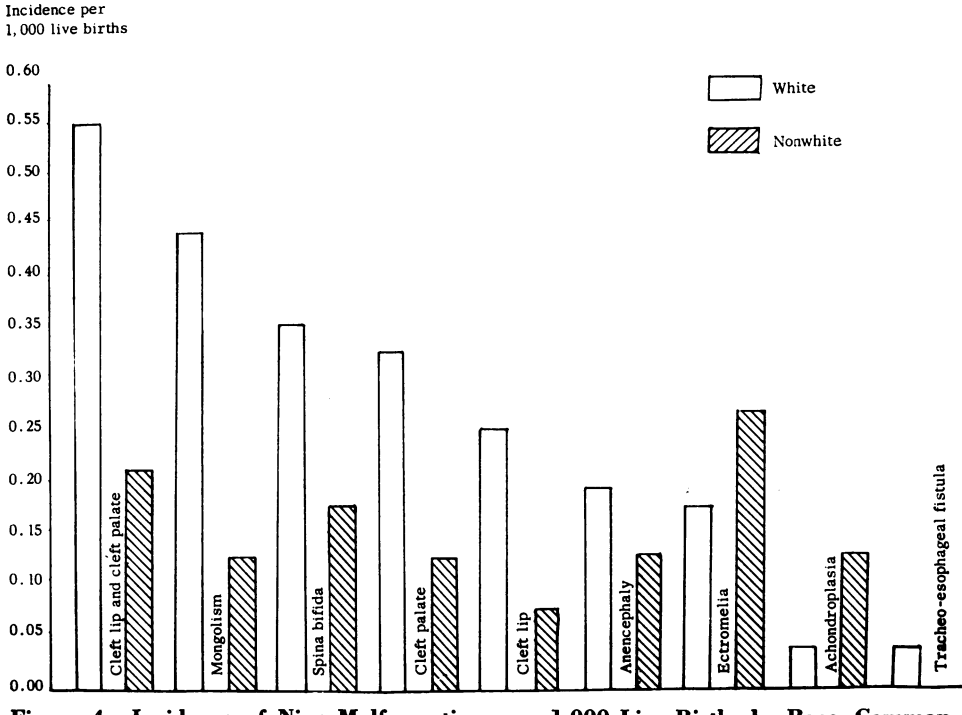

Figure 4—Incidence of Nine Malformations per 1,000 Live Births by Race, Commonwealth of Pennsylvania, March-December, 1960

mothers and 29 to nonwhite parents; total births for the period were 204,212. The over-all incidence of the seven anomalies in the white population in Pennsylvania in 1960 was 2.4 per 1,000 live births, whereas the rate for the nonwhite population was 1.3 per 1,000 live births. As shown in Figure 4, significant differences were noted between the two groups for mongolism, cleft lip, cleft palate, and cleft lip and palate combined, the ratios of white to nonwhite being 3.4, 3.2, 2.5 and 2.5, respectively.

Expanded studies are needed to test the comparability of reporting in different hospitals for white and nonwhite residents of the state. If, on a genetic basis, nonwhites give birth to fewer anomalous offspring, one would expect lower rates in areas having predominantly nonwhite populations. The study just reported for Philadelphia County indicated the opposite to be true.

Discussion

Many years of experimental work with laboratory animals in the field of teratology have led to the establishment of certain well known principles. For example, timing of a teratogenic stress in relation to gestational age is known to be of critical importance in the type of malformation induced. Dosage of the teratogenic agent, agent specificity, and the genetic constitution of the laboratory animal are other critical factors involved in the experimental induction of anomalies. This kind of laboratory experimentation, and the study of naturally occurring epidemics of anomalous offspring in higher mammals, such as cyclops in sheep,[6,7] offer background material to investigators attempting to unravel the etiologies and epidemiologies of animal congenital malformations.

The development of principle cannot be mapped out with such clarity for investigators of the human scene. However, one consistent observation among human populations serves as a lode star, so to speak. Healthy pregnancies are in general associated with the birth of healthy offspring. In fact, this is the basis of modern obstetrical practice. The converse is also well known. Unhealthy pregnancies are more likely to be associated with offspring at the lower end of the biologic gradient of health—disease, i.e., abortion, miscarriage, stillbirth, prematurity, neonatal death, and malformation.

Further confirmation of these generalities is not needed. Rather, the challenge to clinical investigators is the detailed study of specific malformations to determine their specific mechanisms of production. This will require identification of multiple genetic and environmental factors having teratogenic influence.

The field studies reported here were designed with these objectives in mind. They involve case history reviews of certain specific malformations, a beginning attempt to determine distribution by time, by place, and by person, and an inquiry into sources of data.

One principle to come out of these several pilot studies is the importance of specificity. It has been confirmed many times by animal experiments that all anomalies can be no more treated as a single universe than can all nutritional diseases, for example. Although anatomically the lip is near the palate, and the spinal cord begins at the base of the brain, cleft lip, cleft palate, spina bifida and anencephaly behave differently from one another epidemiologically. It is not illogical, therefore, to look for multiple causes by studying the natural history of each defect both separately and in relation to others.

Conclusion

The problem of congenital malformations in human communities is one of

the new frontiers in medicine. Six pilot field investigations reported here represent attempts to explore in the area of prenatal developmental pathology where the challenge is to detect teratogenic agents, and to determine the epidemiology and pathogenetic aspects of specific malformations. As such knowledge is obtained, specific, preventive measures can be included in maternal and child health programs.

A beginning can be made by restricting effort at first to those anomalies which can be identified at birth, by directing attention to the accuracy and completeness of reporting, by prompt field investigations of reported cases, and by combining service programs with investigative efforts aimed at evaluating the respective roles of environmental and genetic factors leading to their occurrence.

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The authors are associated with the Henry Phipps Institute and the Department of Public Health and Preventive Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

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