This presentation consists of several short stories from personal experience to illustrate the complementary nature of epidemiologic and laboratory research in the study of congenital malformations.

Visual Acuity

The Child Health Survey in Hiroshima and Nagasaki from 1958 until 1960 was concerned with a comprehensive examination of about 3500 children born of parents who were cousins and an equal number whose parents were not cousins (Schull and Neel, 1965). An evaluation of the effects of inbreeding was the primary objective, but there was also a chance to study the influence on health of a wide variety of environmental variables. All children had been examined earlier as controls in an evaluation of the genetic effects of radiation (Neel and Schull, 1956). The later consanguinity study concerned children whose parents had received very little or no radiation exposure. Thus, the effects of inbreeding were not confounded by those of radiation. The children were 5 to 11 years of age at the time of this follow-up examination.

The loss of distant visual acuity—that is, vision of 20/70 or worse in at least one eye—was classified as due to congenital organic defect when some abnormality could be found by external examination of the eye or by use of the ophthalmoscope. When no such defect was found, the visual acuity loss was attributed to refractive error, principally myopia. The prevalence of congenital organic lesions of the eye increased very significantly with inbreeding, from 1.69 per 1000 for children of unrelated parents to 10.01 per 1000 for children whose parents were first cousins. Since the rates of these lesions are normally very low, the risk to the child of a consanguineous mating, even though six times normal, is not very great.

Virtually no refractive errors were found among children under 6 years of age. Those occurring thereafter were considered to be due to myopia. The role of inheritance was implicated in the genesis of this defect by the increase in frequency as the degree of inbreeding increased, by the tendency for cases to aggregate in families, and by the greater rates in Japan as compared with the United States (racial difference?). The influence of the environment early in life was suggested by finding that the risk of myopia was increased among children whose birth weight was less than 2500 grams, as previously found in several studies from Great Britain and the United States, and by the independent tendency in Hiroshima for rates of myopia to be higher among children born during the first half of the year, particularly those born in the spring months (Miller, 1963). There was no relationship of childhood myopia to maternal age or to birth order, to socioeconomic status as indicated by average food.
costs or number of floor mats in the home, to evidence of major disease as revealed by the history or the physical examination, to growth as determined by four measurements, to neurologic or intellectual capacity as indicated by a battery of screening tests, or to dental health or development as indicated by caries rates and average number of primary and secondary teeth erupted. The age-specific prevalence rates of myopia were consistently higher in Nagasaki than in Hiroshima.

The accumulated evidence to date suggests that the defect in childhood myopia is present at birth or soon thereafter and that environmental stresses later in life have little influence on its occurrence. The results of our survey indicate that it would be profitable in the future to investigate the origin of myopia through family studies, well-controlled racial comparisons involving Japanese migrants to the United States, and surveys relating myopia in embryologic and at-birth events. In such studies the epidemiologic approach affords an opportunity to weigh genetic and environmental influences in the genesis of a maldevelopment of the refractive system more easily than can be done in the animal laboratory.

Cytogenetic Defects

The relationship of mongolism to maternal age is an epidemiologic observation first made in 1909 (Shuttleworth), more than 50 years ago. Obstetricians have sensed for decades that miscarriages also increase with maternal age, but documentation was poor until two years ago when a group of statisticians—not obstetricians—showed that miscarriages in the first 12 weeks of pregnancy were three times more common among women 35 years of age and older than among women 20 to 24 years of age (Shapiro, Jones, and Densen, 1962). As in mongolism, the maternal age effect on miscarriages is due to some extent to meiotic nondisjunction, which increases in frequency with maternal age. Recently cytogenetic defects have been found in about 25% of selected abortuses (Carr, 1967).

Three studies have shown that childhood leukemia also increases in frequency with the mother's age at the birth of the child (MacMahon and Newill, 1962; Stewart, Webb, and Hewitt, 1958; Miller, 1963). One may wonder whether this relationship also reflects an influence of non-disjunction in some cases of childhood leukemia. In this regard it would be of interest to compare the chromosomal patterns of leukemic children in remission with respect to maternal age or maternal history of miscarriage.

Study of individual families has suggested that occasionally there may be an unusual recurrence of non-disjunction (Hecht et al., 1964). Thus, in the same sibship one may find that two children have trisomy 21, that one child has trisomy 21, that another has Klinefelter's syndrome, and that another pregnancy resulted in a miscarriage. From individual family histories one cannot tell whether or not these occurrences are due to chance. More conclusive evidence awaits epidemiologic studies which evaluate the frequency of disorders associated with non-disjunction among relatives in families ascertained through a child with a non-disjunctive chromosomal error.

These examples indicate that, in the study of cytogenetic defects, there is a substantial interaction among observations made in the laboratory, at the bedside, and by epidemiologic studies.

Coexistence of Congenital Malformations with Cancers of Childhood

The recognition of the link between mongolism and leukemia has contributed to the understanding of the etiology of leukemia. To afford a similar opportunity in the study of Wilms' tumor, the medical charts of 440 children with this neoplasm were reviewed in a search for an excessive occurrence of specific congenital malformations (Miller, Fraumeni, and Manning, 1964). Six of the children were found to have congenital absence of the iris of the eye, giving a rate of 1:73 as compared with the expected at-birth incidence of 1:50,000. Four of these children had cataracts and a fifth had glaucoma, defects known to be secondary to aniridia. Three of the aniridic children had small head circumferences and mental retardation. Thus, there appears to be a syndrome of Wilms' tumor, aniridia, cataracts or glaucoma, mental retardation, and small head circumference.

Among the 440 Wilms' tumor cases in the series, there were three children with congenital hemihypertrophy contralateral to the Wilms' tumor. In one case the hemihypertrophy was limited to the face and tongue. Congenital hemihypertrophy occurs so rarely that no estimate of its frequency in the population is available.

Of 437 children in our series without hemihypertrophy, 4 had extensive pigmented nevi and 8 had significant hemangiomata (4 of them internal), defects known to be associated with hemihypertrophy. Nineteen of the children with Wilms' tumor had congenital abnormalities of the urinary tract other than hypospadias. There were 4 children with horseshoe kidney, 5 with duplications of the upper urinary tract, 2 with aplasia or hypoplasia of the kidney, and 8 with other urinary tract defects. Among the 223 boys, 5 had hypospadias as compared with 0.6 cases expected, and 11 had undescended testes as compared with 3.3 cases expected.

Recognition of the extensive concurrence of certain congenital defects with Wilms' tumor provides
the opportunity to examine the etiology of the tumor in the light of what is known of the malformations. Shaw, Falls, and Neel (1960) concluded from their statewide study in Michigan that aniridia in man is due to the action of a dominant autosomal gene which is almost completely penetrant and which has few, if any, phenocopies. Of their 82 male aniridics, at least two had hypospadias, and three had cryptorchidism, anomalies found in our study to be excessive among children with Wilms' tumor. On the basis of data from the Michigan study, four of our six cases with aniridia were expected to have an aniridic parent, but none did. If the iris defect was genetically determined, it was due to mutation in our series significantly more often than usual. The possibility exists that aniridia and the associated Wilms' tumor were due to concurrent mutations of different genes, or that the gene leading to aniridia enhanced the expression of an already existent Wilms'-tumor gene complex in the manner postulated by Neel (1958).

On the other hand, in the rat, maternal vitamin A deficiency has induced aniridia, horseshoe kidney, hypospadias and cryptorchidism, a finding which suggests that in man these defects may be due to a single gene with pleiotropic effects or to an environmental agent (Miller, 1966). Despite the very low frequency of congenital hemihypertrophy in the general population, 16 cases have now been reported with Wilms' tumor, 4 with adrenal neoplasms, and 3 with liver neoplasms. In congenital hemihypertrophy there is an excess of pigmented and vascular nevi. These benign neoplasms were also seemingly in excess among our Wilms' tumor cases in the absence of hemihypertrophy. This array of associated diseases suggests a congenital growth excess, a hyperplastic-neoplastic diathesis, which is quite variable in expression.

Although aniridia and hemihypertrophy have not been reported in the same patient and although they apparently have different etiologies and underlying mechanisms, they are alike in having a teratogenic-oncogenic influence on the genitourinary tract, for both have been associated with cryptorchidism, hypospadias, and Wilms' tumor. Further research concerning the origins of any one of the diseases in the constellation associated with Wilms' tumor should provide insight into the genesis of the others and may lead to new clues for laboratory research concerning congenital malformations or neoplasia.

References


