

THE ROLE OF GENETICS AND OTHER PRENATAL FACTORS IN DISORDERS OF CHILDHOOD

Summary of Round Table Discussion

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THE PHYSICIAN interested in the etiology of a disease should always try to ascertain as many etiologic factors as possible, because the causal pathogenic web can often be disturbed from different angles. Although hereditary factors will be the main topic of this round table, we shall stress that they never act in a vacuum. The genes direct the development of the embryo and fetus, but the development depends also upon an environment limited by the mother's body and surroundings.

Certain terms are fundamental to an understanding of heredity:

Chromosomes. The nuclear carriers of the hereditary factors, the genes. Each nucleated somatic cell of a person's body has 24 pairs of chromosomes, each pair carrying hundreds of genes. One member of each pair is derived from the person's mother and one from the father. In the female there are 23 pairs of autosomes (non-sex chromosomes) and 1 pair of like sex chromosomes (X-chromosomes). In the male there are 23 pairs of autosomes and 1 pair of unlike sex chromosomes (one X and one Y-chromosome).

Gene. The particulate biochemical factor responsible for a particular hereditary characteristic. As the genes are carried on the chromosomes, they also *occur in pairs*. Each pair occupies a particular locus on the chromosomes. Genes located at the same locus are termed *alleles*. A child gets 1 member of each gene pair from each parent. Sometimes by the rare event of *mutation*, a gene becomes changed into one that may function abnormally—a "pathologic" gene.

Homozygote. An individual in whom the gene pair in question consists of 2 like genes.

Heterozygote. An individual in whom the gene pair in question consists of unlike genes.

Depending upon the type (dominant or recessive) and location (autosome or sex chromosome) of the gene, several types of inheritance patterns are possible.

DOMINANT INHERITANCE. A dominant gene, by definition, produces its effect in every individual who carries it. It follows that (except for the rare event of mutation) *every affected individual has an affected parent*. The affected person has an equal chance of passing the dominant gene or the normal allele on to each of his children. Thus, *each child of an affected individual has a 50:50 chance of being affected*. Dominant conditions are the easiest ones to uncover in taking the family history of a patient. The ascertainment of affected relatives may be diagnostically valuable, as in families where a history of diabetes insipidus or of hemorrhagic telangiectasia leads to the correct diagnosis in the patient.

RECESSIVE INHERITANCE. A recessive gene, by definition, produces its effect only in those individuals carrying 2 doses of the gene. An affected individual will have received 1 such gene from each parent. If the gene is relatively rare, the parents will usually be carrying only 1 dose of the gene, and hence will appear normal. *Any sibling of an affected individual in such a case will have a 1-in-4 chance of getting the gene from each parent, and thus of being af-*

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fected. It also follows that the trait in question rarely occurs in collateral ancestry, and due to the small size of human families, *usually occurs sporadically*. Individuals related by blood tend to have more genes in common than do individuals in the general population, since the former have ancestors in common. The marriage of related individuals (consanguineous marriage) thus increases the chance of children receiving the same gene from each parent. The rarer the gene, the more important does this factor become. Consanguinity of the parents of a child with an unusual disease suggests, therefore, that the disease may be recessively inherited, and that the possibility of recurrence in siblings should be considered.

SEX-LINKED INHERITANCE. Sex-linked genes are those carried on the chromosomes that determine sex. A recessive gene located on the X-chromosome of a male will always show an effect because there is no corresponding allele on the Y-chromosome to “cover” it. In the female, the gene will produce an effect only if present on both of the X-chromosomes she carries. Thus, all males who inherit the gene will be affected, whereas only the rare female who inherits the gene from both parents will be affected (so, she must have an affected father). Each son of a “carrier” female (bearing only 1 dose of the gene) has a 50:50 chance of being affected, and each daughter has a 50:50 chance of being a carrier. Since an affected male passes his X-chromosome only to his daughters, his sons cannot be affected; his daughters will of course all be carriers. *In other words, a recessive sex-linked condition is transmitted through females, and appears in males.* The condition can be expected to appear in the affected individual’s brothers (50 per cent risk), in the mother’s brothers (50 per cent risk), in the sons of the mother’s sisters (25 per cent risk), or in the mother’s father. Other types of sex-linked inheritance occur if the gene is a dominant gene on the X-chromosome or if it is located on the Y-chromosome (the latter giving rise to father-to-son inheritance).

Examples of these 2 patterns of inheritance are known, though they are rare.

Instead of being so clear-cut in their actions, genes often behave in a relatively erratic fashion. One might say that some pathologic genes have weaknesses. Such weaknesses should be of paramount interest to the physician since they indicate that gene action is not inviolate but may be influenced by environmental factors. An understanding of such phenomena should give hope to the physician, whose job is that of converting all genotypes (genetic constitutions) to the most desirable phenotype (clinical appearance).

In some families, the hereditary trait in question “skips” a generation. The apparently normal individual who is skipped may sometimes be shown to be abnormal by laboratory tests. Thus, in the condition known as multiple exostoses, the grandparent and grandchild may have obvious involvement, but the parent may have minimal involvement evident only on roentgenographic survey. The total absence of the trait in the gene-carrying predisposed individual is called lack of *penetrance*, while the variation in trait severity is termed as variation in *expressivity*. These 2 terms describe degrees of gene action. On the other hand, there are genes which produce different effects in the individuals bearing them. The gene for arachnodactyly represents a good example of this behavior, known to the geneticist as *pleiotropy*. Some individuals will show the arachnodactyly characteristic (long extremities and digits), while others may show or not show this feature but may have various combinations of luxation of the lens, hyperextensible joints, deformities of the spine and chest, degeneration of the media of the aorta, and other abnormal findings, all due to the action of one pathologic gene.

Twins represent an experiment in nature, a chance to evaluate the relative roles of environment and heredity. Twins are of 2 basic types, monozygotic (identical) and dizygotic (non-identical or fraternal). The former are of identical genotype, but this

does not guarantee that their appearance will be exactly the same. Environmental factors start acting as soon as conception has occurred. Thus, it is not surprising to see identical twins (identity verified by blood typing and fingerprint analysis) differ in the matter of having or not having harelip, congenital heart defects, diabetes, or other physical and metabolic traits. Identical twins may have different degrees of vascular connections, thus confusing the picture further as far as intrauterine environment is concerned. The discordant monozygotic twins provide an opportunity to study how environmental factors suppress the action of pathologic genes, and may thus be a guide to therapeutic measures.

The interplay of genetic and environmental factors has also been studied in the laboratory. One such study has dealt with the variable effect of cortisone on the production of defective offspring in various genetic strains of mice. The incidence of cleft palate among offspring in some strains can be greatly increased by the use of cortisone in the pregnant mouse mother, while in others the incidence is only moderately increased. In other words, under different sets of environmental conditions, the genotype can show different expression, and differing genotypes can react differently to the same environmental factor.

Phenocopies are environmentally produced pathologic conditions which resemble known hereditary conditions. Thus, by direct irradiation of the fetus (as happened in Hiroshima and in the unfortunate roentgen therapy of incorrectly diagnosed "abdominal tumors"), or by infection of the fetus with toxoplasmosis, microcephaly may be produced which resembles the genetic type due to a recessive gene. Lack of understanding of such differences between clinical and genetic entities has led to false generalizations and statements in the literature. The geneticist often fails to realize that "entities" in the field of clinical medicine are often merely complexes of signs and symptoms of poorly understood eti-

ology. On the other hand, the clinician may fail to realize that sporadic cases of a particular disease may be hereditary (recessive trait in small families), and that familial cases may be nonhereditary (such as endemic cretinism).

The physician should obtain a careful family history from the patient or his parents. He should ask about conditions in the family relevant to the patient's disease with respect to both heredity and environment. He should list the age, sex, and state of health of the patient's parents and siblings. The presence or absence of parental consanguinity should be determined. Often it is advisable to wait until the second visit, after the patient's confidence has been secured, to delve into what often are family secrets. Family information can be most quickly and accurately recorded on the patient's chart by means of pedigree diagrams, with squares denoting males and circles, females.

This brings one to the clinical application of information relating to the causation of abnormalities. The pediatrician often finds himself in the role of counselor. The arrival of an abnormal infant or the appearance of a disabling disease in a child almost invariably prompts the family to ask about the causation of the condition and the chance of its recurrence in future children. If the condition is a clear-cut hereditary trait which follows a dominant or recessive pattern, then the physician has available the 1:1 and 1:3 risk figures that such patterns exhibit. If the trait exhibits variable penetrance, then adjustments have to be made. For many conditions, no definite inheritance patterns are recognized. Under such circumstances, empiric risk figures are available. Such figures have been obtained by determining the incidence of the condition in later-born siblings in families where the condition has already made its appearance. Thus, it has been found that in the case of central nervous system anomalies later-born children have about a 4 per cent chance of having such an anomaly. The physician must remember that risk figures

in such cases have been based on conditions of heterogeneous etiologies. The decision as to whether the family should have further children is a personal decision, that of the family alone. Factors of importance include the severity of the disease, the amount of desire for further children, the size of the family already accumulated, and the attitudes toward adoption and contraception. The physician can allay fears and guilt feelings by explaining the nature of the etiologic factor. He should keep in mind that the family may well have desirable features that more than balance the undesirable trait.

It must be emphasized that hereditary and incurable are not synonymous terms. Hereditary disorders are being treated by the physician every day. The surgeon repairs harelip deformities. The symptoms of a person with inherited hemolytic jaundice are relieved by splenectomy. The diabetic child is given insulin. Galactosemia is treated simply by removing lactose from the diet. Patients with other hereditary diseases may be less fortunate. Little help can yet be offered the child with muscular dystrophy or the infant with Tay-Sachs disease. At one time it was considered justifiable to dispose of defective infants. In more recent times, sterilization has been hailed as a panacea, but it too has lost support, except for use in special and relatively rare circumstances. The phenomena of variable penetrance and expressivity offer hope that environmental features may be adjusted to modify the expression of genes. All of us must study not only the powers, but also the weaknesses of abnormal genes, and in

this way learn possibly to prevent many hereditary disorders.

Question: Will mutants pass on the abnormal gene to their children?

Answer: Yes, a mutated gene follows the same path of inheritance as did its predecessor.

Question: Are there any hereditary conditions that can be altered by special treatment during pregnancy?

Answer: No, there is no evidence to date that would indicate success of this type.

Question: Can monozygous twins be identified with certainty?

Answer: Well, not exactly. By the use of blood typing, fingerprint analyses, and various physical features, probabilities can be determined. From a practical viewpoint, there are sufficient sets of discriminating characteristics available to permit a near perfect identification of the monozygous pairs.

Question: What do twin studies in mongolism reveal?

Answer: Monozygotic twins have always been reported as concordant for mongolism, whereas dizygotic twins are usually discordant. The distribution of the different types of twinning and sex in these data suggests that errors may well have been made in determining zygosity. It is therefore somewhat difficult to evaluate these data, although they in themselves suggest that heredity may well be of importance. The risk of recurrence in siblings is, however, low, and seems to depend mainly on maternal age.

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