CLASSICAL FORMS OF MENDELIAN INHERITANCE

A knowledge of the classical modes of inheritance is useful both for giving correct genetic advice and for recognizing the inter-relationships between genetic and clinical entities. Identical clinical appearances may be produced by different genes each having its own distinct prognosis. For example, this may be seen in the pigmentary retinal dystrophies (retinitis pigmentosa), the hyalo-retinopathies and the hereditary optic atrophies. Moreover the same gene may produce differing clinical pictures depending upon the effects of other genes or of environmental factors. For example, this is thought to occur in colobomatous defects of the globe, in the van der Hoeve syndrome and in the phakomatoses. Criteria for recognizing the Mendelian forms of inheritance are presented.

Criteria for recognizing Autosomal Dominant Inheritance (Fig. 1)

- (1) There is direct transmission through several generations.
- (2) Every affected individual has an affected parent, unless the result of a new mutation.
- (3) An affected individual has, on the average, 50 per cent. affected children.
- (4) Normal members of an affected family as a rule have normal children.
- (5) Autosomal dominant traits occur with equal frequency in males and females.

There is often wide variability in the severity, or *expressivity*, of a dominant trait. If this expressivity is so reduced that its effects cannot be detected, as occasionally occurs in individuals who have the gene for retinoblastoma, the gene is said to be *non-penetrant*. When non-penetrance occurs, a generation may be skipped (Fig. 1a).

The marriage of two affected individuals results in 50 per cent. of the children being heterozygous and thus affected, 25 per cent. being normal and 25 per cent. homozygous. The homozygous affected state is probably often lethal (Fig. 1b).

FIG. 1.—Autosomal dominant transmission.

(a) II.5 shows non-penetrance, a generation having been skipped.

(b) The marriage of two affected individuals (II.2 and II.3) produces a (presumably homozygous) lethally affected child (III.1).

Criteria for recognizing Autosomal Recessive Inheritance (Fig. 2)

- (1) Affected individuals, who must be homozygous, appear suddenly in one generation, previous generations being apparently unaffected.
- (2) Affected individuals have clinically normal parents, each of whom is a carrier of the recessive gene.
- (3) When both parents are carriers, 25 per cent. of their children will be affected and 50 per cent. will be carriers.
- (4) Affected individuals have clinically normal children who are carriers.
- (5) Autosomal recessive traits occur with equal frequency in males and females.
- (6) The rarer the recessive gene, the more frequently will affected individuals be the result of a consanguineous marriage.

The marriage of an affected individual to a carrier will result in 50 per cent. of the offspring being affected (pseudodominance), while the marriage of two affected individuals will result in all the children being affected.

FIG. 2.—*Autosomal recessive transmission.* A consanguineous marriage between II.4 and II.5 has produced affected offspring. The consanguineous marriage between the affected male III.10 and the carrier female III.11 has produced affected offspring (pseudodominance).

Criteria for recognizing X-linked Recessive Inheritance (Fig. 3)

- (1) Affected individuals are usually male.
- (2) Father-to-son transmission never occurs.
- (3) Affected males usually have clinically normal parents, but the mother must be a carrier.
- (4) Affected males frequently have affected maternal uncles, great-uncles, or male cousins.

The marriage of a normal male and a carrier female produces 50 per cent. carrier and 50 per cent. normal daughters, and 50 per cent. affected and 50 per cent. normal sons. The marriage of an affected male and a normal female produces carrier daughters and normal sons. The marriage of an affected male and a carrier female produces 50 per cent. affected and 50 per cent. carrier daughters, and 50 per cent. affected and 50 per cent. normal sons.

In many (so-called) X-linked recessive conditions the carrier females show minor abnormalities (intermediate sex-linked transmission). This is particularly true in choroideremia, in one genetic form of pigmentary retinal dystrophy and in ocular albinism.

This article is designed to be the key to future contributions in this series of genetically-determined ocular disease.

FIG. 3.—*X-linked recessive transmission.* The carrier females, I.2, II.2, and II.3, have produced carrier and normal female offspring, and affected and normal male offspring. The affected male II.4 has produced a carrier female and a normal male. The union between an affected male III.6 and a carrier female III.7 has produced affected and carrier female offspring, and affected and normal male offspring. The affected male IV.7 received his abnormal gene from his mother.

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