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# SYSTEMIC OPHTHALMOLOGY

CORNEAL GRAFTS - Edited by B. W. Kythort, O.17. N.O., BIGMS, I.R. C.

Edited by

ARNOLD SORSBY

SECOND EDITION

PRINTED AND BOUND IN CREAT SENTEN BY LOVE AND MALCONSON, LTD. REDSOLL SURREY

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(Ophthalmology)

OPHTHALMOLOGY

CORNEAL GRAFTS-Edited by B. W. RYCROFT, O.B.E., M.D., D.O.M.S., F.R.C.S.

GENETICS IN OPHTHALMOLOGY-ARNOLD SORSBY, M.D., F.R.C.S.

MODERN PRACTICE IN OPHTHALMOLOGY—Edited by H. B. STALLARD, M.B.E., M.A., M.D., F.R.C.S.

MODERN TRENDS IN OPHTHALMOLOGY—(Third Series) Edited by ARNOLD SORSBY, M.D., F.R.C.S.

ARNOLD SORSBY

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# PREFACE TO THE FIRST EDITION

In the preface to the fourth and last edition of his classical *Medical Ophthal-moscopy*, published in 1904, Sir William Gowers explained that "when this book was first written twenty-five years ago the subject with which it deals was more familiar to physicians, who constantly used ophthalmoscopy, than to ophthalmic surgeons. . . . It is, I believe, a fact that such a book as this, at the time it appeared, could not have been produced by any other than a physician, but cannot now be kept abreast of general and special knowledge except by the joint efforts of a physician and an ophthalmic surgeon." It was for that reason that he sought the collaboration of Marcus Gunn.

Since Gowers' days, Medical Ophthalmoscopy has expanded into a highly developed special study of its own. Largely owing to historical accidents, the neurological and ophthalmoscopic aspects were heavily emphasized, but subsequently the study came to embrace the medical aspects of eye disease generally. This development led to the broader designation of Medical Ophthalmology, and ophthalmologists have contributed to it no less than the physicians or neurologists. In fact such systematized texts on Medical Ophthalmology as have been available for many years have been the work of ophthalmic surgeons. But the designation Medical Ophthalmology has in turn become too narrow, for the general aspects of eye disease carry surgical, obstetric, metabolic, dermatological and other implications no less than those of a purely medical character. It is for this reason that the more comprehensive term Systemic Ophthalmology has been used for this book.

The field is now so wide as to be beyond a single-handed effort by either a physician or an ophthalmic surgeon. It is hoped that the collective work here presented reflects adequately current teaching and aspirations.

August, 1951.

ARNOLD SORSBY

# PREFACE TO THE SECOND EDITION

THE CALL for a second edition has made it possible to revise the whole of the text and to incorporate entirely new chapters on subjects where advance has been particularly rapid. I am indebted to my collaborators for readily helping in pruning both text and illustrations, so that in spite of the additional material the present edition has not grown in size.

ARNOLD SORSBY

London January, 1958.

The fare John L. Prenderson - Revised by Ruby Joseph

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# CLINICAL ASPECTS and performance bed to be a laid of

THE CLASSICAL division of congenital anomalies into environmental and hereditary forms is largely valid, though many malformations are probably produced by the interaction of both hereditary and environmental factors. In any particular case it is often impossible to be certain of the origin of the affection: cataract in rubella is not in any way different from hereditary cataract; buphthalmos, whether genetically determined or of environmental origin is very much the same: optic atrophy leads to the same degeneration of nerve, and to the same blindness, whatever the case. In fact, as far as appearances go, diseases of environmental origin may be phenocopies of genetic disease—a faithful reproduction in the soma of one individual of a genetically determined lesion observed in another.

Hereditary factors

As the complexities in the transmission of genetic disease have become revealed, it has become obvious that the significance of heredity in malformations is considerable, and many affections previously unsuspected of being genetic in origin have in fact been proved to be of this type. As against the obvious direct transmission from generation to generation, known to the older observers—the dominant inheritance of present-day genetics—there are such less obvious modes of inheritance as sex-linkage, and the apparently "sporadic" case that may occur with recessive autosomal inheritance or with a new mutation. The appreciation of irregular dominance, and of such concepts as penetrance and expression, have emphasized still further the significance of hereditary influences. How complex these can be is shown by the fact that in human pathology there are well-established modes of inheritance (such as that seen in Leber's disease, or in the transmission of an affection to succeeding generations of women) for which there is no ready theoretical explanation. The full significance of heredity in congenital disease, therefore, still remains to be assessed.

Environmental factors d bearach a salizmons to no detailment but noticeborg add

In contrast to genetically determined disease, in which each parent is of equal significance, the effect of environment on the developing embryo is largely a matter of the maternal influences. Whilst there is no evidence that environmental factors are transmitted by the sperm, maternal environment is of obvious and immediate concern to the embryo over the whole of its existence. Such vague clinical features as maternal malnutrition have been held responsible for congenital anomalies; it has been reported that following famines the incidence of stillbirths, monsters, and various foetal anomalies is increased. Chronic ill-health in the mother has also

### THE NATURE OF MALFORMATIONS

been blamed. There is more definite evidence that maternal diabetes, especially diabetes of the juvenile type persisting for several years, is deleterious, for the incidence of foetal loss and of serious abnormalities in the offspring is greatly increased. Older concepts, such as abnormalities in the amniotic fluid, including the formation of amniotic bands, are unlikely to be valid to any substantial extent, if at all; they are of some interest in that these mechanical explanations tend to be revived from time to time, as in the recent view that malposition in the uterus produces "compression abnormalities"—a faint echo of an older view which ascribed achondroplasia to insufficient amniotic fluid.

Three associations of congenital anomalies are based on more definite clinical evidence. There is considerable evidence that radiation of the pelvis of a woman during the early stages of pregnancy is apt to lead to miscarriage or malformation, sometimes gross. Likewise there is evidence that a high maternal age is a significant though not exclusive factor in mongolism, the offspring of ageing mothers being particularly prone to show the disturbance, whilst primogeniture appears to be a factor in congenital pyloric stenosis. Much the most definite clinical evidence centres on infection.

Two distinct issues arise. First, there is transmitted maternal infection as seen in congenital syphilis; here the pathogen itself is transmitted through the placental barrier, and, depending upon the severity of the infection, there is miscarriage, still-birth or a viable infant with clinical lesions at birth, in infancy, or later in childhood. In contrast there is the congenital anomaly seen in the offspring of a woman who has contracted rubella early in pregnancy; here the pathogen has passed through the placental barrier and actually damaged the developing embryo—there is no suggestion of the pathogen lying quiescent in the developing embryo. It is this that other virus diseases may occasionally act in the same way, and that the later stages of pregnancy are also susceptible. The exact status of the congenital anomaly produced by toxoplasmosis is not clear. Toxoplasmosis is a sub-clinical affection in the mother; the parasite passes the placental barrier; it lodges in a particular tissue, such as the retina or choroid, or the brain, and produces pathognomonic destructive and irritative reactions of a localized character.

Interaction between hereditary and environmental factors

Mongolian idiocy is a classical clinical example of this. The affection is genetically determined, but tends to become manifest mainly in the offspring of ageing mothers—the variable maternal environment of the developing embryo apparently prevents or precipitates the genetic potentiality. The mass of experimental evidence on the interaction of environmental and hereditary factors in the production and manifestation of anomalies is discussed below.

# PATHOLOGICAL CONSIDERATIONS

# Genetic anomalies

Developmental history

A genetically determined anomaly does not arise as a finished process; it has a developmental history of its own. This is clearly seen in studies on the mouse both with congenital defects and abiotrophic anomalies.

#### PATHOLOGICAL CONSIDERATIONS

Congenital defect: anophthalmos.—The course of development in this congenital recessive affection is shown in Fig. 1. Development proceeds normally half-way through pregnancy, when no further differentiation occurs and regressive changes set in. Anophthalmos is not inherited as such but results from an inherited

inability of the optic vesicle to grow to maturity.

Abiotrophic anomaly: retinal dystrophy.—At birth the mouse retina is undifferentiated into its various layers. These become apparent by the eleventh day after birth. In retinal dystrophy—a recessive affection simulating human retinitis pigmentosa—development proceeds normally till the eleventh day and all layers of the retina are differentiated. But whilst in the normal mouse further post-natal development occurs in the rods, as shown in Fig. 2 a-d, no such finer differentiation occurs in the dystrophic strain (Fig. 2 e-g). On the contrary, regressive changes set in. Prior to the occurrence of these regressive changes the retina is normal only to a superficial view: in fact it shows the mildest of congenital defects—arrest of development in the terminal stages of post-natal development. Retinal dystrophy in the mouse, as also in the rat and the Irish setter, therefore represents a developmental anomaly in which the regressive changes occur in post-natal life instead of in intra-uterine life as with anophthalmos.

Presumably human retinitis pigmentosa which shows essentially the same features as retinal dystrophy in the mouse, rat and setter, is also the sequel of an "unfinished" retina. This assumption is supported by the facts that abnormal electoretinography findings and night-blindness precede ophthalmoscopically visible changes—the retina in retinitis pigmentosa has probably never functioned fully.

The origin of genetic anomalies

Several factors have been isolated:

Mutants.—It is assumed that every biological innovation begins as a mutant form of an existing trait. Mutations occur "spontaneously" and, on the whole, rarely. Genes are essentially stable and transmitted unchanged over generations. The tendency to spontaneous mutation varies with each gene, so that each gene has a mutation rate of its own. Whether a mutation—once it has occurred—becomes apparent at once or over several generations, or perhaps not at all, depends upon whether the mutant gene is dominant or not. Recessive autosomal mutants will become manifest only in the homozygous state, whilst recessive sexlinked genes also require appropriate conditions. Many agents, x-rays and nitrogen mustards in particular, are "mutagenic", but there is evidence that they speed up the rate of mutation rather than actually induce mutations. There is also evidence that a mutation represents a change in one ion in the complex molecular structure of the gene.

Maternal environment.—That maternal environment is a significant factor in the manifestation of genetic disorders has been shown experimentally by two sets of observations. First, there is the frequency of an anomaly in the offspring in relation to maternal age; thus, in the guinea-pig, the occurrence of polydactyly in a polydactylous strain is highest in the offspring of young mothers; in a piebald strain the size of white areas on the coat increases with increasing maternal age. Secondly, there are observations in which particular anomalies are more common in breeding experiments in which it is the mother who happens to carry the

#### THE NATURE OF MALFORMATIONS

anomaly. Thus, the "C57 black" strain of mouse almost constantly shows 5 lumbar vertebrae, and the C3H strain almost always 6 such vertebrae; in crosses between such strains, the frequency of 5 lumbar vertebrae is considerably higher

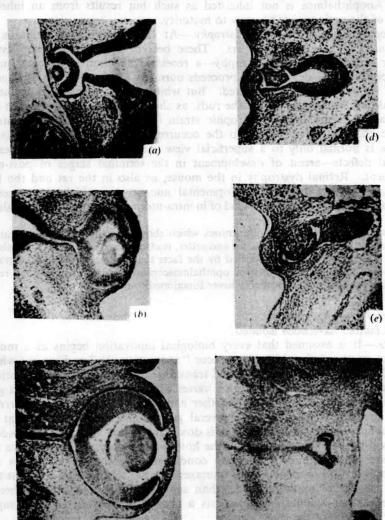


Fig. 1.—Congenital defect: hereditary anophthalmos in the mouse from disturbance in development (×60). Note progressive development in the normal control and the increasing regression in the affected strain. (After Chase, H. B., and Chase, E. B. (1941). J. Morph., 68, 279.)

Control:	At: 1600 cm	Anophthalmic strain:
(a) Left eye	10 days 23 hours	(d) Left eye
(b) Right eye	11 days 20 hours	(e) Left eye
(c) Right eye	13 days 2 hours	(f) Right eye

# PATHOLOGICAL CONSIDERATIONS

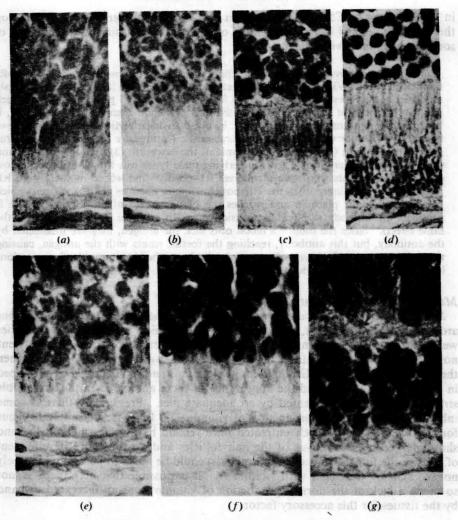


Fig. 2.—Recessive retinal dystrophy of the retinitis pigmentosa type in the mouse. Postnatal development of rod and outer nuclear layers of retina in normal and affected mouse.

(a), (b), (c) and (d). Development in normal mouse at twelve, fourteen, twenty-one and twenty-eight days. Note that whilst rod and nuclear layers are already differentiated at twelve days after birth, there is considerable post-natal development so that at twenty-eight days the rods are clearly differentiated into two segments.

(e), (f) and (g). Development in affected mouse at eleven, thirteen and fourteen days. Note that in contrast to normal mouse post-natal development beyond eleventh or twelfth day, there are rapidly developing regressive changes in the rods. At twenty-eight days, when normal retina has reached full development, rods and outer nuclear

layers in affected mouse are completely degenerate.

In retinal dystrophy in the mouse, which genetically and histologically simulates human retinitis pigmentosa, the evidence is therefore that, whilst the retina becomes differentiated into its various layers, the rods do not develop fully. The tissue is "jerry built" and degenerative changes set up in tissue that has never been normal. (After Sorsby, A., Koller, P. C., Attfield, M., Davey, J. B., and Lucas, D. R. (1954). J. exp. Zool., 125, 171.)