Genetics and Ophthalmology

VOLUME I

Genetics and Ophthalmology

by

P. J. WAARDENBURG M.D. Former Lecturer in Medical Genetics
University of Utrecht and Leyden (The Netherlands)

A. FRANCESCHETTI M.D. Professor of Ophthalmology
University of Geneva (Switzerland)

D. KLEIN M.D. Professor of Human Genetics
University of Geneva (Switzerland)

1961
ROYAL VANGORCUM, PUBLISHER ASSEN, NETHERLANDS
BLACKWELL SCIENTIFIC PUBLICATIONS LTD., OXFORD
CHARLES C THOMAS, PUBLISHER

The publication of this volume was made possible
through a grant from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)

Printed in the Netherlands by Royal VanGorcum Ltd., Assen

Preface

Many years ago an up-to-date version of my textbook 'Das menschliche Auge und seine Erbanlagen' was planned by professor Franceschetti and me. As the material to be dealt with had shown a tremendous increase since 1932 we agreed to divide the subjects in two approximately equal parts. We could not then foresee that my collaborator, though extending our knowledge in this field by private research and by theses achieved under his supervision, would not find the time required for the systematic composition of a work such as we had in mind. Thus I had to take over several more chapters, and automatically the editorship devolved on me. After the co-optation of professor Klein the work went forward. I am happy to be able to say that besides the valuable contributions to this volume, my collaborators will cope in a third volume with important chapters, dealing with stationary functional defects of the retina, progressive neuro-retinal abiotrophies and a number of neuro-ophthalmological disorders or syndromes.

An attempt has been made to divide the subject matter into purely ophthalmological and neuro-ophthalmological parts. This could however not be consistently maintained, if by the latter we mean affections of primarily neurogenic origin and by the former any defect originating in the peripheral organ. For one thing one is not always sure (e.g. in congenital alacrimia) and then again there is good reason not to separate the groups too strictly. It is expedient to deal with neurogenous heterochromia in Vol. I, because in this way the various types can immediately be compared. Recent data make it probable that they have a similar origin and should therefore be moved to Vol. II in a second edition. This difficulty also applies to some hereditary affections of the conjunctiva (as in the Holthuis - Biemond - Van Bolhuis Syndrome) to types of cataract or microphthalmia in so far as they are associated with neurological defects. There is often a strong case for assuming a primary ectodermal correlation instead of a primary neurogenic origin for the various symptoms. Regarding muscular deviations the separation is as far as possible maintained, but it would not be surprising if my classification of complicated retractio bulbi in Vol. I would in future prove to be untenable. Everything in the way of classification and grouping is bound to be more or less artificial, because the living organism continually breaks through the boundaries imposed by didactic considerations. General albinism and ocular albinism have been included in the chapter on Membrana Uvea, this being the first tissue of the eye in which the characteristic pigmentation defect becomes conspicuous. Thus the usual classification of the hereditary affections of the eye into those of the separate tissues and those of the eye as a whole has been relinquished, except for Total Refraction in which axis-length and lens play an important part, and in which various tissues are involved. Hydrophthalmia and glaucoma have been dealt with in a separate chapter on the Anterior Chamber. The one on Eye, Orbital Region and Face contains several new syndromes.

Chapter I begins with some notes of historical interest winding up with the mentioning of the work of the pioneers who in the frame of their time and with the limited means at their disposal laid the foundations on which posterity could build. At the request of many colleagues then follows a brief summary of general genetic problems elucidated as far as possible by examples from ophthalmology, and the latest discoveries about chromosomes, genes, mutations and chemisms; also some elementary statistical and biometrical notions, indispensable for population genetics and the ascertainment of conclusions in general. It winds up with an extensive survey of non-hereditary causes of embryopathias and phenocopies in the field of ophthalmology and of the extent and importance of twin research, the results of which have been put at the end of each paragraph throughout the book. It is clear that in most cases the recorded numbers are as yet much too small to draw statistically valid conclusions.

Data and literature on occasion go far back into the nineteenth century, to a period prior to the development of modern genetics. That is because it has been found, that even at that early time many accurate observations were made that fit into present-day schemata. Moreover a good deal of attention is given to embryology, comparative teratology, hereditary affections of the eye in animals, and to racial differences in modern and prehistoric man. Furthermore the pathological and also the anthropological characteristics of the eye are dealt with, knowledge of which matters may be valuable in paternity questions. The reader will find besides the pedigrees a selection of family histories to enable him to criticize or corroborate our provisional conclusions. Our statistical data require completion or revision.

For students desiring to work in the field of human genetics I might recommend the examination of descendants of well-documented affected families, in order to find out whether the disorder has died out or is still transmitted. Our knowledge of the mutation rate can be improved by looking for genetic relationship between similarly affected families spread over the country.

When the Harvard System was adopted all the self-made abbreviations of the literature had to be brought into line, which turned out to be a most time-consuming item.

Dutch family names like Van der Hoeve, Van Dijk, De Groot can be found under H, D and G.

Double names are registered under either the first or the second name.

The Japanese authors who are not mentioned in the bibliography can be found in Taku Komai (1934): Pedigrees of hereditary diseases and abnormalities found in the Japanese race, Kyoto (Japan). I could not mention the authors of the pedigrees taken from Komai's Report No. II (1934-1943), Hokuryokan, as their names were printed in Japanese.

Acknowledgements

Towards the end of the Second World War the loss of the greater part of my library made it seem impossible for me to continue my scientific work. But the generosity of Dr. E. Sørensen at Copenhagen, who after the decease of his wife, Dr. Ruth Lundsgaard, gave me her ophthalmological library enabled me to start again. I am also much indebted to professor Riddell of Glasgow, as well as to Swiss friends, among whom were professor Hanhart and professor Schlaginhaufen and some oculists who provided me with literature.

I am very grateful to the many colleagues both at home and abroad who were found willing to supply information, photo's and cliché's. Their names are recorded at the corresponding places.

My special thanks are due to professor J. Francois who never failed to send a prompt reply to questions concerning Belgian publications and who permitted me to reproduce parts of his chapter on 'Notions de Statistique et de Biometrie'.

Professors Colebrander, Hagedoorn and Van den Heuvel also helped me in various ways, and I am extremely grateful to them.

I was glad to find that several members of O.O.G.[1] and others put some time at my disposal for the collection of valuable family data.

I must acknowledge my special indebtedness to Dr. J. Schappert-Kimmijser by whose initiative an anthropogenetical working committee of oculists was formed, and to Dr. H. E. Henkes to whom I owe many E.R.G.'s. Their observations and suggestions as well as those of Dr. E. B. H. de Haas at our numerous conferences on the prevention of blindness have been very stimulating.

It is difficult to express adequately my indebtedness to Dr. J. C. Burg (of Nijmegen) for the excellent drawing of the pedigrees that provide so useful a visual counterpart to the text.

My constant appeals to Miss R. G. Prak of Leiden to check difficult data from literature have never been made in vain.

Here I wish to express my great appreciation of the work done by the publishers, Van Gorcum and Co., and their staff. They have borne patiently with my exacting demands and have taken many cares off my shoulders and have done their utmost to carry out my wishes.

The publication of my work would not have been possible without the generous subvention of Z.W.O. (Organization for the Advancement of Pure Research). Also during the long years of preparation I was glad to receive financial support from Z.W.O., the Netherlands Federation for Anthropogenetics and the 'Drie Lichten' fund to defray the technical expenditure involved. For all this help I am very grateful.

The above is an attempt, however inadequate, to acknowledge my debts. Apology is here tendered for any inadvertent omission which over a long course of years seems to be inevitable.

[1] O.O.G. stands for 'Oostelijk Oogheelkundig Gezelschap, one of the two regional Dutch Ophthalmological Societies, neither of which publish an account of their transactions.

Contents

Chapter I - Genetics and the Human Eye

by P. J. WAARDENBURG

I. HISTORICAL INTRODUCTION

1. *The earliest conceptions of heredity of eyetraits and some other characters*

Eyetraits

WE owe a great deal of our knowledge regarding the history of ophthalmology to HIRSCHBERG (1899).

Ophthalmology had a curiously slow development. Except for a temporary flourishing among the Arabs, it was more or less dormant until the 19th century. It is therefore one of the younger branches of medical science. In the present century however, it has not only caught up with other branches, but as a result of HELMHOLTZ's discovery of the ophthalmoscope (1850) it has surpassed them in accuracy of diagnosis. It has also helped internal medicine and neurology to make a correct diagnosis at an earlier moment. Most important of all, *it is the first branch of medical science which has contributed on a large scale to human genetics.*

On looking backwards we find that the *Ancient Greeks and Romans* already had some knowledge of the heredity of eyetraits, in contrast to the Hammurabian Code in Mesopotamia. The following quotation from the corpus Hippocrateum is conclusive (Hippocrates lived from 460-377 B.C.): 'if bald people are descended from bald people, people with blue eyes from people with blue eyes, squinting persons from squinting persons, at least in the majority of cases, what is to prevent macrocephalics being born of macrocephalics'? (by macrocephalics who were regarded as superior people he probably meant what we now call dolichocephalics). Hippocrates obviously lived among a mixed population where blue-eyed offspring came not only from blue-eyed parents but also from blue-eyed and brown-eyed or from two brown-eyed hybrid parents.

Homer knew the great similarity between parents and children (see his identification of Telemachus as the son of Odysseus).

Congenital *nystagmus* – then called 'hippus' – was also known to the Hippocratean school, but heredity of this trait or of myopia is not mentioned.

Myopia has been described by ARISTOTLE (384-322 B.C.) who did not mention its heredity either. He knew that it was accompanied by elongation of the axis of the eye. He thought the colour of the eyes to be normally black, while blue eyes represent a kind of deficiency in the shade (now known to be recessive). ARISTOTLE argued that parents and children not only show likeness concerning congenital disorders but also as regards some disorders acquired during lifetime. He states that *blindness* and lameness are transmitted by the parent to the offspring (MAYER 1953). Moreover he gives an instance of heredity from grandfather to grandson by the unaffected mother (GEURTS l.c. p. 112), so skipping a generation (X-chromosomal heredity?).

No statement comparable to that in the Greek world is found in the Old Testament about the *Hebrews*. No special comment is made about the fact that Jacob (Gen. 48 : 10) *became blind in old age* as did his father Isaac (Gen. 27 : 1). We know neither what kind of blindness this was, nor whether it was inherited. In 1937 I put forward the suggestion

that *a fair complexion in Jews can partly be traced back to the Palestine Hebrews*. On Egyptian monuments, the Mitanni (1700-1500 B.C.) and the Amurru (Amorites) both in Palestine and the Near East (1400-1300 B.C.) are represented as having fair hair and blue eyes. Intermarriage with the Jews may have taken place on quite a large scale and may account e.g. for the fair complexion and high stature of King David.

In the New Testament *congenital* blindness is mentioned, but only in isolated cases. PLINIUS (23-79 A.D.) records the family of Lepidé, characterized by an eye anomaly noticeable *through several generations*, but with some interruption (discontinuous heredity).

PLUTARCHOS (50-125 A.D.) described homochronous *heredity of blindness* in old age as in the case of Isaac and Jacob, and in a greater number of descendants (the Timoleon family in Corinth).

AETIUS (540 A.D.) distinguished between myopia with and without enlargement of the eyeball, and he was the first to describe the appearance of congenital ocular *dermoids*.

PAULUS of AEGINA (607-690 A.D.) erroneously mentions *strabism* and myopia as congenital anomalies.

ARISTOTLE and GALENUS (130-210) both knew of *presbyopia*. DONDERS however was the first to explain hypermetropia, differentiating it from presbyopia. The hereditary anomalies of colour vision were not mentioned before the end of the 18th century.

Heredity in general in Antiquity

GEURTS (1941) quotes a passage from the Corpus Hippocraticum, which proves that *mental* characters and physical *diseases* may also be hereditary.

The assumption of some modern geneticists that even fathers may contribute to the *conception of twins*, is supported by the history of Jacob who was one of binovular twins (Gen. 25 : 24-26) and of his son Juda, who begot twins by Thamar (Gen. 38 : 27). *Decreased fertility* was the fate of Sarah, Rebecca and Rachel who were related to each other. The book of Chronicles gives an account of the inheritance of *giantism* (1 Chron. 20 : 4-8) in Philistean kindreds (father and 4 sons, one with polydactylism; Goliath and his brother Lachme (2 Sam. 21 : 19-22). There are reports of the great stature of the Enakites (Num. 13 : 28, 33), Amorites (Amos 2 : 9) and Sabeans (Jes. 45 : 14), and it is well known that the Philistines and Aethiopians, in contrast to the average Jew, were tall.

The belief in the great influence of circumstances and in the inheritance of individually acquired characters

The story of Jacob, who outwitted Laban by succeeding in having his sheep conceived while they were looking at mottled reeds, so that they brought forth ring-streaked, speckled and spotted offspring, suggests a vague allusion to some sort of fantastic exogenous influence during the time of conception (force of maternal impressions?).

Both the Hebrews and the Greeks believed in the inheritance of individually acquired characters. In the Old Testament it is however twice noted – Ezech. 18 : 1, 2 (7th century B.C.) and Jerem. 31 : 29 (6th century B.C.) – that, contrary to the usual hereditary interpretation of the second commandment of the law of Moses, mentioning that the sins of the fathers will be visited even upon the third and fourth generation (Ex. 34 : 7), only the trespassers themselves and not their children would incur divine punishment and that the actual situation was not as expressed in the proverb: 'the fathers ate sour grapes and the children's teeth are on edge.' This was obviously the general opinion in the ancient Orient, for Hippocrats assumed that if the parent had undergone an operation the offspring would inherit the resulting condition. This idea persisted and was elaborated in a theory by de LAMARCK (1809). DONDERS, one of the greatest pioneers of ophthalmology, though unacquainted with de Lamarck's doctrine,[1] declared in 1848, in his otherwise magisterial opening lecture: 'We saw that *each trait acquired by the individual* is transmitted to the offspring.' (The Harmony of Animal Life,

[1] FISCHER and TEN DOESSCHATE (1958) in their biography of F. C. Donders p. 100 report his saying: 'although the communications of Lamarck were as unknown to me as to almost everyone in that period,' and so they assume his statement of 1848 to have been his own opinion.

Revelation of Laws p. 19.) HIRSCHBERG (1899) refuted this idea because he had seen from experience that patients successfully operated on for squinting, had had children who started squinting at the same age as they had done themselves. He also mentions that the practice of circumcision for generations did not change the sexual organ of the offspring. The theory of de LAMARCK is completely refuted by modern geneticists – except for a time by Lysenko in Soviet Russia – both by logical argument and owing to the fact that the results of all experiments are negative.

2. *Eugenical proposals and practical measures*

Most of the measures proposed or taken in the course of centuries lacked a sound basis because there was no knowledge of the laws of heredity (e.g. Linnaeus' difficulty to fit the 'Homo monstruosus' into his system).

The custom of the Spartans (Lykurgos) of getting rid of children with inborn malformations by throwing them into a cleft near the Taigetos, will doubtlessly have rooted out some hereditary disorders, e.g. anophthalmia.

Speculation and intuition, more than exact observations have more than once led to utopies concerning ideal states e.g. those of PLATO (428-347 B.C.), THOMAS MORE (1478-1535), the Italian monk THOMAS CAMPANELLA (1568-1629) who published his book 'Civitas solis' in 1620, or to other projects, like those of LOUIS BONAPARTE for the Netherlands.

The proposals were often too rationalistic and too harsh for those who were born with unfavourable qualities. They made little allowance for ethics and the need of personal freedom.

In later years PLATO took back many of the radical ideas uttered in his youth.

DESIDERIUS ERASMUS of Rotterdam (1466-1536) in his 'Dialogues on the Perfect and the Unequal Marriage' advocated the dissolution of a marriage if defects had been kept secret. MORE's proposal (1516) to examine the physical condition of engaged couples was more practical.

Among the Jews marriage with an epileptic woman was forbidden and according to MAIMONIDES (1135-1204) a Jewish bride and bridegroom were examined by relatives before marriage. In Sweden in 1734 and in 1757 the marriage of epileptics was prohibited by law; this law was valid till 1915. The famous hygienist and founder of population politics JOHANN PETER FRANK (1745-1821) who lectured in Germany, Austria, Italy and Russia and published his 'System einer vollständigen medizinischen Polizey' was the first medical scientist who propagated that marriage between *very degenerated*, dwarfish and very crippled people should be prohibited! Louis Bonaparte during his short government of the Netherlands (1806-1810) planned the prohibition of marriages of malformed persons and proposed – very curiously – to facilitate their emigration to the colonies and on the other hand to forbid immigration or even a lengthy residence of such people in the country.

So the famous anthropologist FRANCIS GALTON (1822-1911) who in 1883 introduced the term 'eugenics,' in correspondence with Homer and Sophocles who used the word "eugenes", was not the first to propagate legal measures.

3. *Attitudes concerning consanguineous marriages during the past centuries* (eugenically non-intentional and intentional measures)

Legal limitation and prohibition of consanguineous marriages – in the light of our present knowledge – are also means of prevention of hereditary blindness and other disorders. We do, however, not know which laws were based upon this consideration, because law like religion has its roots in the distant past. The public opinion of various peoples in different ages condemned these marriages.

It is not at all evident, as has often been supposed, that the Old Testament prohibitive laws and penalties for trespassers (Levit. 18 and 20, Deuteron. 18, 23 : 20) refer to marriage. Contemporary theologians interpret the Hebraic text as meant for sexual intercourse and also for the sake of decency. Union or unchastity between the following near relatives was forbidden: son and mother, grandfather and granddaughter, full and half brother and sister, nephew and aunt from father's and mother's side, nephew and uncle's wife (aunt related by marriage), father and daughter-in-law, brother and sister-in-law (brother's wife) and in addition a polygamous relation of a man with two sisters or with a mother and her daughter or granddaughter. We wonder why sexual intercourse or marriage between grandmother and grandson, uncle and niece or between cousins are missing in this list.