Physiology. — *"On the Heredity of Keratoconus and other Deformities of the Eye."* By Prof. J. VAN DER HOEVE.

(Communicated at the meeting of June 28, 1924).

Since the revival of MENDEL's law, the subject of heredity has attracted a large amount of attention among biologists.

No property of plants, animals or men, but was subjected to the question: is it hereditary or not? and if it is: does it follow MENDEL's law?

In botany this may be readily ascertained, as there is unlimited scope for experimentation under the most favourable conditions for the development of the property under consideration.

Animals also may be experimented on for this matter, but whoever tried to do so is fully aware, that great difficulties block the way, especially when higher animals are concerned.

With man experimentation in this domain is precluded altogether; one has to confine oneself to the material that nature bestows upon us in the families, in which some property or deviation is hereditary. An attempt is then made to establish a pedigree of these families, as far as this is possible under the circumstances.

Ophthalmologists have been making such pedigrees for many years, and have not confined themselves to physiological properties, but they have also concerned themselves about morbid anomalies such as glaucoma, cataract, keratoconus, etc.

For most of these diseases it is easy to establish their heredity; it is much more difficult, however, to ascertain whether the anomaly follows numerical rules such as MENDEL's. All sorts of difficulties will crop up:

1°. The material differs largely as to quantity: it is very abundant in cases of myopia, mostly very scanty in recessive diseases, so that we often have to content ourselves with a few pedigrees.

2°. Outside influences may come into play so as to retard, nay even to inhibit the appearance of that hereditary anomaly in spite of the presence of the hereditary factor.

3°. The hereditary anomaly does not always appear already at birth, it may come forth even very late in life, the so-called homochronous nheritance; so senile cataract occurs late; generally it does not get

ripe before about the 65th year; it is evident that many individuals of a family in which this anomaly occurs, will have died before it has been established, so that the numerical relations are considerably modified.

4°. The hereditary deviation does not always result directly from the hereditary factor, but may be its remote consequence, so that influences may play a role here that otherwise would not assert themselves.

5°. It may very well be possible that an hereditary property does not arise from one and the same hereditary factor alone, but from a combination of several of them, so that, while the hereditary factor may obey certain laws, the deviation cannot be expected to do so on that score.

6°. One and the same hereditary anomaly may occasionally be brought on by different hereditary factors and by outside influences. Some instances taken from ophthalmology may illustrate this.

Boephthalmos i.e. the presence of an abnormally large eye, may occur:

a. as a direct outcome from the hereditary factor; prodigious growth of the eye, so that a large, but for the rest quite normal, eye is developed.

b. as an indirect consequence of the hereditary factor: the absence of the canalis Schlemmii. This may induce a rise of pressure with secondary dilatation of the eye-ball. Notwithstanding the presence of this hereditary factor the eye may retain its normal size, when the other efferent ducts duly supply the place of Schlemm's canal.

c. as a mediate result from other hereditary factors, such as bad condition of the other efferent ducts for the liquid; too copious a secretion of the eye-liquid and the like.

d. caused by outside influences (so-called peristatical), e.g. iritis with seclusio pupillae and consequent rise of pressure.

It is evident, therefore, that boephthalmos is engendered by various hereditary factors and peristatically, while it may be absent even when an hereditary factor is present. Moreover, already in intra uterine life boephthalmos may bring on atrophy or perforation of the eye, so that the individual is not born with an large eye.

It may be readily understood that under these circumstances the numerical rules can hardly be recognized.

Tetany-cataract, i.e. a cataract as a complication in tetany, may be hereditary. As to its genesis this still unproved theory has been advanced: The primary cause is anomaly of the glandulae parathyreoideae which evokes spasm, a.o. of the ciliary

muscle; these spasms injure the epithelium of the ciliary body by which the secreted liquid, which serves for nutrition of the lens, is modified, so that cataract is originated. It is obvious that the presence of the hereditary factor: anomaly of the glandulae parathyreoideae, does not at all induce tetany-cataract in all cases. The same degree of this factor will produce spasm of the ciliary muscle in one individual, not in the other; the same spasm of this muscle will cause lesion of the epithelium with one individual, but not with the other; the same modification in the eye-fluids will elicit cataract in one lens, not in the other. So if the hereditary factor acts according to fixed rules, these rules will not of necessity be observable in the cataract appearing as its remote effect. It is more a matter of surprise that the inheritance of cataract can be established than that it does not follow the rules.

Nowadays senile cataract is also considered as being hereditary, while there is a tendency to ignore other influences on its origin. But I know a family of whom the members that live in Europe, have to be operated upon for senile cataract at the age of 65, whereas the members that have long lived in India came to operation at the age of 47. Heredity alone does not account for this.

In my theory on the etiology of cataract one of the chief causes is the modification of the ciliary epithelium under the influence of light with many ultraviolet rays. Strong lightsources of that kind will reveal in animals a modification of the eye-liquids inside of a quarter of an hour; a more prolonged radiation will elicit severe inflammation of the corpus ciliare.

In my judgment the ciliary epithelium so well guarded by outside walls is injured from within, the lens being optically heterogeneous, not optically empty, so that part of the light is dispersed diffusely, also in the direction of the corpus ciliare. This dispersed light contains comparatively many ultraviolet rays, because the dispersion is always stronger for rays of a short wavelength. According to RAILEIGH'S law the dispersion is even inversely proportional to the fourth power of the wavelength, so for ultraviolet of 300 $\mu\mu$ about 50 times stronger than for red of 800 $\mu\mu$.

Since a large dosis of it evokes acute inflammation, it may be that radiation by sun-, and day-light prolonged for years, brings about an inappreciable change, which by modifying the nutritive liquid for the lens may excite senile cataract.

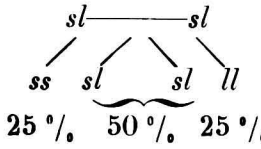
Now the hereditary factor may be marked opalescence of the lens, which differs very much individually. Besides this optical heterogeneity light with many ultraviolet rays is also required, so that

we see that, in the family alluded to, the members in India, who are exposed to much light, contract a cataract much earlier than the members living in Europe. A still more effective protection of the eye would perhaps retard the appearance of the disease so long that it would not reach maturity.

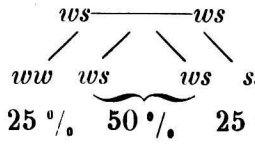
A disease elicited by more than one hereditary factor is myopia. It is brought about by a disproportion between the refraction, which is relatively too strong, and the axis of the eye, which is relatively too long.

Since the investigation carried out by COHN at Breslau in the middle of last century, myopia has chiefly been ascribed to working at short distance-vision. In that time fears were even entertained that through this sort of work the intellectuals would eventually incur blindness. About ten years ago STEIGER has called attention to the fact that the long since recognized hereditary moment in the appearance of myopia was largely underrated. He believes that the length of the axis and corneal refraction are hereditary factors, each in their own way. An examination of 50000 corneae brought to light that the corneal refraction in emmetropic persons is liable to considerable physiological variations and STEIGER reasoned in this way: if an emmetropic eye has a cornea that refracts 5 D. more than normal, the length of the axis must be proportionately shorter; if the refraction is 5 D. weaker than normal, the axis must be longer in the same proportion.

Now let us take the case of two emmetropic persons with a normal length of the eye-axis, because a long and a short hereditary factor are present in them, with whom also the refraction of the cornea is normal, because a strong and a weak hereditary factor are present, which counterbalance each other. If these persons are united in marriage, the eye-axis of the offspring will, according to MENDEL'S law be short in 25 %, long in 25 %, and normal in 50 %:



For the corneal refraction the values are 25 % strong, 25 % weak and 50 % normal:



In $^1/_{16}$ of the offspring the weak refraction will coincide with the short eye-axis, so that an intense hypermetropia will manifest itself; in $^1/_{16}$ the strong refraction will coincide with the long eye-axis, consequently a high degree of myopia will appear.

This reasoning induces us to assume that coincident with physiological varieties in the corneal refraction of 5 D. on either side of the normal physiological varieties in the refraction may be expected from 10 D. hypermetropia to 10 D. myopia.

In this case the laws of heredity will not be very conspicuous, as far as myopia is concerned, though their course may be followed for corneal refraction.

The great significance ascribed to heredity has given rise to a threatening danger, viz. that the presence of hereditary deviations is looked upon as a mere fatalistic fact, and no effort is made to prevent or relieve the disease. This I consider to be a mistake. Since outward circumstances can play such an active part in the occurrence of the deviations, we may exert some influence by modifying those outward circumstances. In cases e. g. of incipient myopia it is incumbent on us to improve as much as possible the circumstances that may also be answerable for the lengthening of the axis of the eye.

From the foregoing it will be inferred, that we have little reason to expect an hereditary deviation in man to follow MENDEL's law. It should, moreover, be borne in mind that in plants and animals this law holds only for averages out of large numbers.

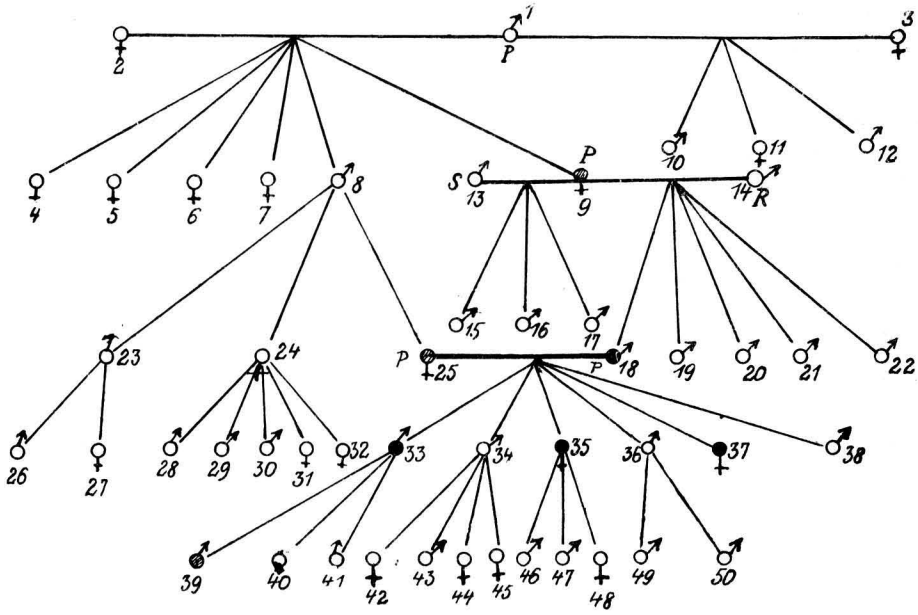
This may be expected in man with some reason, in those hereditary anomalies which are congenital, not subject to the influence of external circumstances, and cannot be caused peristatically, e.g. the typical redgreen-colourblindness. We can, indeed, clearly distinguish in this affection the type of the recessive hereditary anomaly limited by sex.

A rare instance of deformity is keratoconus, in which at a certain age, most often after the 10th year, sometimes not before the 40th year, the spherical shape of the cornea is transformed into a conical one, consequent on a peculiar decrease of the resistance of this tissue.

Whether this deformity is hereditary or not, is still a subject of uncertainty. The annexed pedigree (see fig. page 652) illustrates the keratoconus as probably a typically recessive disease, whose frequency will increase through marriages between blood-relations.

N°. 33 of the pedigree I have known since twenty years suffering from bilateral keratoconus. Inquiries and investigations made

out that not only two sisters were affected with the same deformity, but also the father N°. 18, who had been operated upon for it by Prof. DOYER at Leyde already in 1869. DOYER seemed already



then to have surmised the possibility of heredity. Anyhow, in the historia morbi he noted down the visual acuity of the man's parents N°. 9 and N°. 14, for the mother respectively $^2/_6$ and $^2/_3$ of the normal, for the father $^2/_3$ and normal. It would seem then as if the man had inherited the deformity from the mother; although in her case DOYER did not diagnose keratoconus, yet he notes that the fundus oculi is abnormally elongated. It is certain, therefore, that this woman was astigmatic, was perhaps affected with keratoconus. Now the question was: why half of the children, procreated by 18, suffered from keratoconus? On inquiry it appeared that this man had married a cousin german (25). This family-marriage accounted for the increase of the cases of keratoconus; but husband and wife bore the same familyname; it seemed, therefore, that it was a paternal relationship on both sides, whereas we supposed that the husband had acquired the deformity from the mother's side.

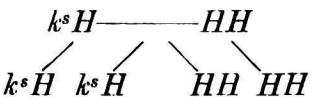
Inquiry and painstaking research-work at the registrar's office yielded the following results:

Mrs. P., N°. 9, was married to Mr. S. N°. 13, by whom she had three children; she wanted to be divorced. S. refused and she then lived in free union with R N°. 14, by whom she had five children (18—22). Legally she was obliged to give notice of the births of

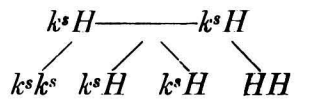
these five children as the legitimate husband's, but she had no mind to do this. She could not have them registered as the real father's (R), so she gave them her own name. This illegal action of N°. 9 caused that 25 and 18 had the same name, although their kinship originated from the father of the one and the mother of the other.

This is an illustration of another difficulty in establishing numerical rules for heredity in man. It is not only that a single instance of conjugal infidelity may render our pedigree valueless, but even a permanent illegitimate relation, such as that between 9 and 14, may escape our notice, if the woman had had her children christened S, according to the law.

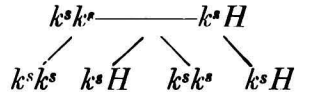
When surveying the whole pedigree it occurs to me, that the case under consideration is a typically recessive anomaly. In one of the progenitors 1 and 2 the hereditary factor keratoconus was latent. He marries a healthy woman, and according to MENDEL's law transmits the latent disease to 50 °/₀ of the children, in this case to



8 and 9. 8 transmits it again as a latent disease to half of his children, decidedly to 25. 9 has 5 children by 14. Now we have to assume that also R harbours a latent keratoconus factor. Then according to MENDEL's law 25 °/₀ of R's issue will have homozygous



manifest keratoconus. This tallies with the fact that one of the five children, N°. 18, has keratoconus. N°. 18 marries N°. 25. Of their



issue, according to MENDEL's law, 50 °/₀ must reveal homozygous i.e. manifest and 50 °/₀ heterozygous i.e. latent keratoconus. This agrees with the fact that 33, 35 and 37 have keratoconus.

Of the next generation none of the children will suffer from homozygous keratoconus; all the children of the keratoconus-sufferers 33, 35 and 37, will have heterozygous latent keratoconus; of the children of the sufferers from heterozygous keratoconus, 34, 36, 38 only the one half, while the other half will be quite normal in this respect.

If in adult life one of the children of this generation evinces manifest keratoconus, this must be ascribed to another keratoconus factor in the other parent of this child, which factor may be searched for in this parent's relations. This research will by no means always be successful, since a recessive hereditary factor may remain latent in a family for 100 years or more, unless a member of this family marries somebody who harbours a similar recessive hereditary factor.

Two more questions remain to be answered:

1°. How is it that 9 and 25 are astigmatic? It is possible that the combination of the hereditary factor keratoconus with a healthy factor, does not produce keratoconus, but that the healthy factor does not absolutely dominate, so that astigmatism appears. If this be true most of the children of the generation 39—50 must become astigmatic.

2°. What is the hereditary factor here? Is it a direct deficiency of resistance of the cornea, or is it, as SIEGRIST believes, a morbid „Anlage" of the glandulae thyreoideae which engenders dystheroidismus, from which a secondary keratoconus might arise. The patients examined for this did not display symptoms of dystheroidismus, but in 33 and 39 the ABDERHALDEN-reaction, which was tested for all the endocrine glands, was highly positive for the thyroid only.

In cases where dystheroidismus is presumably the hereditary factor, the process may be arrested by preparations from endocrine glands.

To sum up, it is most likely that we have to do here with a typically recessive homochronous hereditary anomaly.