ON THE HEREDITY OF EYE CONDITIONS

a

Thesis

submitted to Glasgow University for the

Degree of Doctor of Medicine

by

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November 1939.

On the Heredity of Eye Conditions.

Contents.

Synopsis.

In part one the heredity of myopia,night-blindness and retinitis pigmentosa in association with other defects is discussed. This serves as an introduction to the second part which is concerned with search for genetic linkage relationships in families inheriting both haemophilia and colour-blindness. In the third part three large pedigrees of blue sclerotics,brittle bones and deafness are described. In the largest of these colour-blind individuals were found. This pedigree was examined in detail for blood-group and taste factors in an attempt to establish linkage relationships. The last section is based upon the investigation of five hundred consecutive patients examined primarily for errors of refraction in whom the condition of the ear lobes and iris colour was recorded. A short analysis of this material is made and the section concludes with a pedigree in which all these normal factors were investigated. The thesis is concluded with a note upon the problems discussed and the need for further work on these lines.

Pedigree Charts.

" For I believe that, while theories are transitory, a record of facts has a permanent value."

Sir James G. Frazer .

On the Heredity of Eye Conditions

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Introduction.

This thesis is based upon the numerous examples of hereditary anomalies which have been observed in various ophthalmic clinics. The material is arranged in order of increasing complexity,commencing with a discussion on the heredity of myopia and ending with an attempt to investigate families segregating for both normal and pathological factors.

There are two main methods of acquiring knowledge concerning the heredity of eye conditions. One is the collecting of statistics and pooling the data ; this may be called the biometrical method. The other is the collection of family histories and the study of the relationships between the individuals concerned. As sciences heredity and genetics are concerned with the establishment of general laws and the individual member of an affected family is of little moment. To the clinician who is interested in these matters the individual aspect is constantly

recurring. I have been very much impressed by the interest which members of various families have shown and the lengths which they will go to in order to be of assistance. Without such co-operation the larger pedigrees included in this thesis could not have been investigated fully at all. Clinically the thoroughness with which a pedigree is enquired into may depend upon the practical aspect of a particular case. Unhappiness may be caused by full enquiry, or even by informing the individual of the cause of his disability. An impressionable boy rejected by the Navy on account of colour blindness is better to believe that his ideas of colour are a little peculiar or that the standard is very high, rather than to be told that he is red-green blind and that his mother is responsible for it.

Geneticists frequently complain that clinicians tend to publish only the "interesting cases", such as pedigrees which contain a large number of affected individuals. While this criticism has a certain basis of truth, it is not possible to report in detail every pedigree encountered. An ophthalmic clinic would never finish if the heredity of each refractive error was investigated; a patient with Leber's disease may attend for some months before the condition is diagnosed, and so on.

Knowledge concerning the heredity of plants and animals can be obtained by direct experiment. The science of genetics is essentially an experimental one. In the study of human heredity indirect methods have to be employed such as the mathematical analysis of human populations and the study of human pedigrees. Such material is frequently fragmentary and always laborious to collect.

Modern genetic theory is a particulate one and assumes that inheritance is controlled by hereditary factors called genes which are transmitted from one generation to another. It is factors which are inherited not characters. The transmission and behaviour of genes is the same in man as in other species although curious differences do occur. For example every medical student learns that haemophilia is a sex-linked condition which is transmitted through the female to the male and that there are other conditions which may behave in a similar way. With the exception of the gene responsible for the production of the yellow coat colour in cats, no sex-linked gene is known to occur in mammals, although extensive study of the heredity of domestic and laboratory animals has been carried out for many years (Ford 1938).

From its very nature investigation of this type is dependent upon the work of others and the co-operation of observers in other parts of the country. Twelve pedigrees are included in this thesis ; six of them have not been published before ; four have been worked out by myself and have appeared in various publications ; two had been published previously by other authors and have been brought up to date by myself.

No attempt has been made to give a comprehensive survey of inherited eye disease. The approach is that of a clinical ophthalmologist to the problems presented and the work itself has raised more questions than can be answered. A child is brought to a clinic by a myopic mother anxious for advice. Until the question is investigated the type of inheritance of myopia is unknown in relation to a given family. It may appear to be due to the action of dominant, recessive or sex-linked factors ; it may be associated with night-blindness, a high incidence of detachment of the retina and so on.

Implicit in a great deal of teaching to students and of instruction to patients is the impression that

myopia can be controlled by environmental factors such as nutrition, use of the eyes and the wearing of glasses. Most clinicians would agree that an under-nourished child of myopic stock living in poor conditions, is more likely to develop the secondary effects of myopia than a healthy child living in good conditions. But the relationship of nature and nurture with regard to this problem is not clearly defined.

Knowledge increases by the inter-play of abstract subjects such as mathematics and genetics with the more obviously practical subjects such as clinical medicine. The clinician provides the raw material in the form of clinical histories and pedigrees, the genticist sorts out the significant data and the statistician applies the refinements of mathematical technique. This was the method by which the two forms of Leber's disease were differentiated (Bell 1928). More recently clinicians have been asked to augment their information with blood samples for grouping purposes and other data. The investigation of these additional factors have two main objects. One is the elimination of any question of environment

affecting the hereditary aspect of the matter. The blood group to which a person may belong is quite independant of his nurture and his social surroundings, but is related to the tribe or nation to which he may belong.

The second object is the possibility of establishing genetic linkage relationships for both normal and pathological hereditary factors in a given pedigree. The theoretical possibility of establishing such linkage measurements in man was shown by Bernstein in 1931. Genetic linkage in man was measured for the first time by Dr.Julia Bell and Prof. J.B.S.Haldane in 1937. Their work was based upon pedigrees in which both haemophilia and colour-blindness occurred and will be referred to in detail in this thesis. The significance is that if a colour-blind individual is also a haemophilic in a pedigree in which close linkage can be shown, then most of his haemophilic relations will also be colour-blind. Conversely if he is colour-blind but not a haemophilic, then most of his haemophilic relations will not be colour-blind.

If similar linkage relationships were to be found in other connections practical answers might be given to the questions of our patients. For example the myopic mother who brings her child for advice as to the probability of his developing myopia might have her fears allayed if it could be shown that in that particular family the presence of myopia was linked with a non-pathological factor. If the child could be shown not to carry this factor then the probability would be that myopia would not develop.

Modern genetic theory is based upon complex mathematical probabilities on the one hand and the chromosome theory on the other. No attempt has been made in this thesis to summarise these aspects of the problem. Ophthalmology has got relations with many branches of science of which the clinician has only got a superficial knowledge. It is possible to discuss questions relating to glaucoma without entering into the technical details of the thermodynamical balance called the Donnan equivalent, and it is hoped to discuss certain aspects of genetic linkage without critical knowledge of Bernstein's formulae or understanding of such terms used by

cytologists as preheterokinesis and postacrosyndesis.

Many developments have taken place since the clear cold evening in February 1865 described by Iltis when several men were walking along the Johannesgasse in Brünn (Brno) towards the Modern School. One of these men was Pater Gregor Johann Mendel of the Altbrünn Monastery of St.Thomas and he was going to address the Brünn Natural History Society on his "Experiments in Plant Hybridisation". There were forty members present at the meeting and the paper was published in the Transactions of the Society.

The importance of this pioneer work was not realised until 1900 when the well known re-discovery of Mendel's work was made sixteen years after his death.

"I had long tried to gain some insight into the relative powers of Nature and Nurture, in order that due allowance might be made for Environment, neither too much nor too little, but without finding an adequate method of obtaining it."

Francis Galton (1822-1911).

Part I.

Section I.

Myopia.

"Progressive short sight is in every case ominous of evil for the future" (Donders 1864). This sentence appears on the title page of the famous book on the Hygiene of the Eye written by Hermann Cohn. He investigated 10,060 school children in Breslau and district and his work formed the basis of the modern systematic eye sight testing in schools. This work was published in 1867 and it influences clinical ophthalmology to this day. He held that myopia arose as a result of prolonged close work and that the schools were primarily responsible for this. He showed how myopia did not appear until the children had been at school for some time and that it increased as they grew older. He regarded myopia as the result of environment and although he devoted a chapter of his book to the influence of heredity, his conclusion was that the question of the heredity of myopia was not yet decided; that the transmission of the tendency to myopia was at least highly probable, but that in very many cases, without any hereditary

predisposition, myopia was developed from other causes.

It is probable that myopia involves both heredity and environment. This may be expressed in the form of a table ; -

Child A	Good Heredity	Good Environment	Emmetropia.
Child B	Bad Heredity	Good Environment	Low Myopia.
Child C	Good Heredity	Bad Environment	Low Myopia.
Child D	Bad Heredity	Bad Environment	High Myopia.

The difference between child A and child B is assumed to be a genetic one ; that between child A and child C an environmental one. All forms of treatment are designed to bring children C and D into the A - B group. Clinically it is frequently assumed that children such as B and D have the same chances as A and C in the struggle against environmental factors and that all we need do is to give them "equal chances"and all will be well. It is becoming more widely realised that B and D are destined to become myopic from the start. In all such cases the time spent on enquiry into the family history may be of great practical value. A boy with a low hypermetropic reserve and a family history such as is shown in Pedigree Chart A would be ill advised to decide to go to sea because in the early twenties he might be unable to reach Board of Trade visual standards. This

opinion would be based upon his heredity and not upon his environmental conditions. The Annual Report on the Medical Inspection of School Children published by the Corporation of Glasgow for the year ending July I938 contains an instructive table in Appendix IV. A portion of it is reproduced below.

" Non-Rouine" Examinations of Pupils in Two High Schools "

	Age	Height	Weight	Visual Acuity		
	Yrs. Mns.	Ins.	Lbs.	Good	Fair	Bad
2 High Schools	I3 7.9	6I.2	97.5	77.2	I0.2	I2.6 %
Other Glasgow Schools	I3 5.3	57.4	83.7	77.6	I4.8	7.5 %

From this it is seen that the High School boys are on the everage 3.6 inches taller and I3.8 pounds heavier than their non-fee paying contemporaries. The incidence of "Good" vision expressed as a percentage is practically the same in both groups, whilst more boys are reported to have "Bad" vision in the fee paying schools. These figures might suggest that as the environment at home of the High School boys is better than that of the poorer children the additional height and weight is thus accounted for and that vision developed independently of the environment. On the other hand it is quite possible that in an industrial area the difference might

be entirely due to selective factors at work in the population. The larger and heavier individuals tending to obtain more responsible positions and so "get on" in their world, assisted by the undoubted advantage of a low degree of myopia for studious purposes, with the result that their children could be sent to fee-paying schools. That such a suggestion is not entirely fanciful may be seen from the study made by Wallace and Travers (1937) upon a group of speciality salesmen. This study was similar to others carried out in America where it was found that the more agressive and self-assured type of individual tended to get on and that employers were inclined to promote the taller and heavier individuals.

The Glasgow figures might be taken as evidence in favour of the view that refractive errors are entirely under genetic control and are unaffected by environment. It is doubtful if any ophthalmologist would subscribe to this extreme view because of the known sequelae of high myopia. It is obvious that an eye liable to the secondary changes of myopia is in a much worse position to resist such changes if the environment is bad. Bad environment includes more than under nourishment. Myopic boys with athletic ambitions frequently take to sports such as swimming, running, boxing and fencing rather than

games which involve moving objects at a distance such as cricket and tennis. The boxing ring is a bad environment for a myopic eye. It is quite possible that as in the case of cretinism, we have a sporadic and endemic form of myopia over and above the division suggested by some observers of a physiological and a pathological form.

Table I is taken from Cohn's figures and in the light of knowledge not available at the time, they are of great interest. They show that myopia does not appear until adolescence to any great extent. Cohn and his followers attributed this to the evil effects of close work. If myopia is attributable to recessive hereditary factors which are wide-spread in the population the theoretical incidence would be 25 % . The fact that myopia may not appear until the second decade does not invalidate this. For example Huntington's chorea is undoubtedly due to hereditary factors and the average age of onset is 35.5 years (Bell I939). In the two gymnasia investigated by Cohn the incidence of 26.2 % is highly significant.

These classical investigations were followed by similar studies all over the world. In I885 Randall collected the published records of I46,522 examinations of school children. The result of these accumulated statistics was to prove that myopia

Table I.

	Percentage of Myopia.
Five Village Schools	I.4
Twenty Elementary Schools	6.7
Two Higher Girl's Schools	7.7
Two Intermediate Schools	I0.3
Two 'Realschulen'	I9.7
Two Gymnasia	26.2

I0,060 Children, I004 with Myopia - 9.9%

was rare in infancy, seldom present at the beginning of school life, and that as education advanced there was a diminution of hypermetropia and an increase of myopia. All this work led to very great improvements in school design. Buildings, school-rooms, desks, books, and lighting were all improved and there can be little doubt that even if 'school myopia' is not a disease, it has served a very useful purpose.

Donders' opinion was that "In fact the predisposition is almost invariably congenital, and in that case it is, moreover, nearly always hereditary. Beer, Jänken, Böhm, von Hasner, and many others, have referred to its hereditary nature: I believe, even, that from time immemorial the conviction thereof has been general among the people. At least, at present the patients are accustomed at once to state, that their father or mother was near-sighted, and that the same condition was found among brothers and sisters. I cannot, with any accuracy, give the proportion in which hereditary cases occur; but this I may say, that where I found near-sightedness in one or more of the children, and had an opportunity of examining both parents, I only exceptionally saw M wholly wanting in both, while on the other hand, when one and equally when both parents were myopic, the predisposition almost always passed on,

at least to some of the children perhaps more especially to the younger (v.Artha). Experience shows further, that where only a trace of M. is present in youth, it inevitably becomes further developed, and that the greatest care leads to nothing more than limitation of the degree."

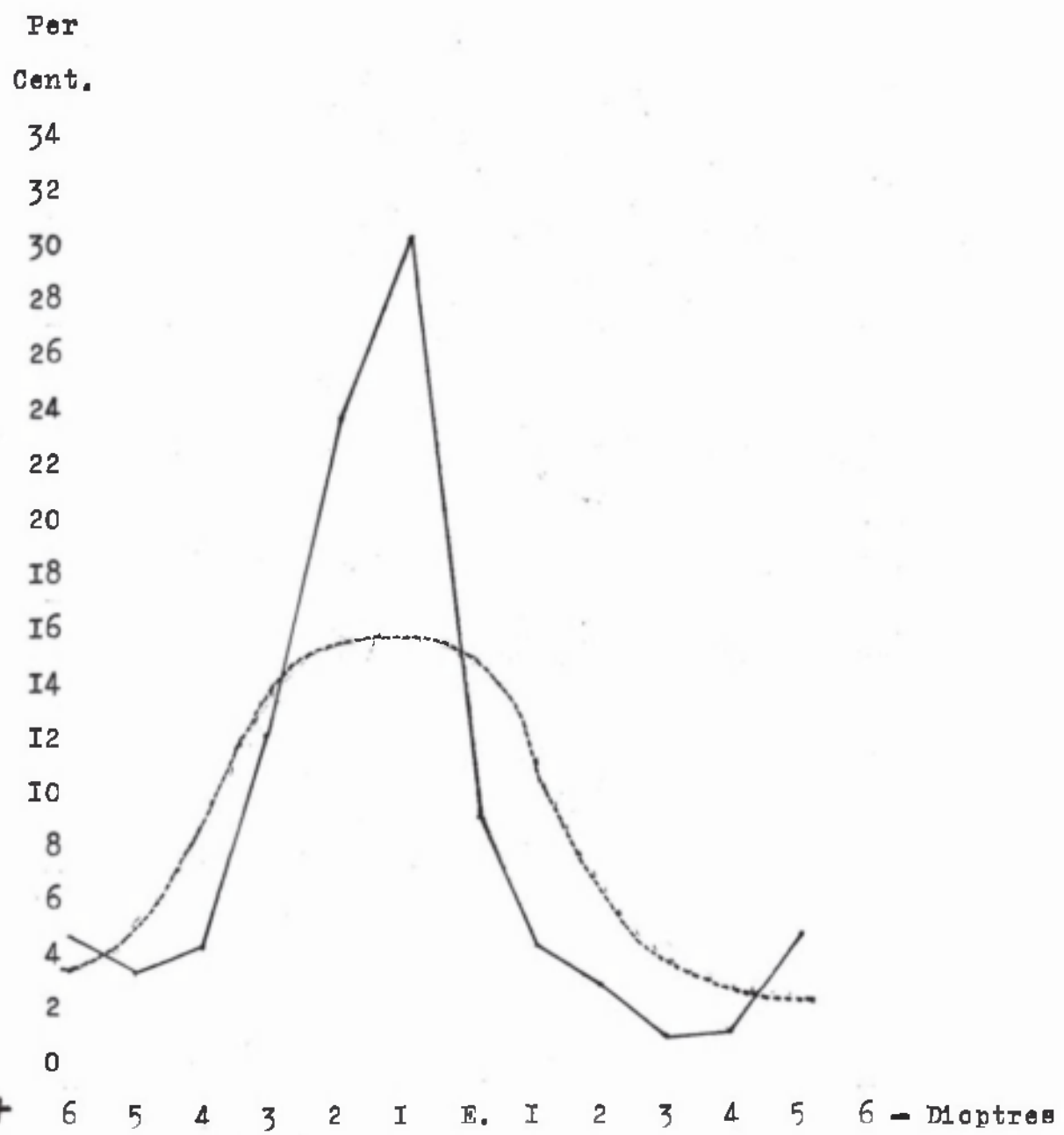
The idea of a hereditary predisposition was also held by v.Arlt who wrote in 1876, "Short sight itself cannot be looked upon as hereditary, but only the tendency to short sight."

For nearly fifty years the matter remained as it was until 1913, when Adolph Steiger of Zurich published his book, "Die Entstehung der sphärischen Refraktionen des Auges". Steiger brought forward the view that errors of refraction may be considered as hereditary biological variations, which may be fitted into a binomial frequency curve. His view stated briefly was, that just as there are tall and short individuals, there are long and short eyes: that the refraction depends on three variables, the axial length of the eye, the dioptric power of the cornea and of the lens; and that, if these are three variables, refraction curves should fit a theoretically derived binomial curve. As originally stated his views are untenable, but have led to a reconsideration

of the whole matter. "The reorientation that has occurred of late years with its change of emphasis from the mechanistic to the biological approach, has evolved a method of study rather than a solution of the problem of myopia". (Sorsby 1938).

The difficulties of Steiger's views may be illustrated by the refraction polygon shown in Fig.I. This is based upon my examination of 704 patients, between the ages of 40-60. The two meridians of each eye were plotted separately as suggested by Dunstan (1934). The figures are derived from 341 private patients refracted in the ordinary manner and 363 insured patients refracted by means of Wright Thomson's skiascope. Both sets were examined without a mydriatic and as there was a doubt in my mind about the validity of the second method, this was investigated and proved to be satisfactory for the purpose (Riddell 1939a). The curve as it stands has no absolute value for the reasons that are operative against all such investigations, the material is not unselected and the investigation was not carried out under full mydriasis. A free hand binomial curve is indicated by a dotted line. This curve illustrates the two main objections to the full acceptance of Steiger's views. There is a peak around 2.0 and I.0 D. and there is a definite bias towards the myopic side with an actual rise

Figure I.



Continuous Line - Refraction polygon constructed from data relating to 704 patients. Each meridian was recorded separately so that an individual patient contributed four measurements, making 2,816 in all.

Dotted Line - Free hand binomial curve.

(Hitherto unpublished).

at the end. Table II shows the figures relating to the refraction of various age groups made by different observers. It is modified from Dunstan (1934) and my own figures are added. The result of the study of such curves has been the suggestion that there is a physiological and a pathological myopia. This view cannot be hastily rejected and more careful study of the heredity of myopia may throw more light on the matter. It is known for example that there are myopic pedigrees which contain more retinal detachments than can arise by chance. Changes in calcium metabolism may affect the myope detrimentally and so on. The construction of refraction curves has focussed attention on the two points which prevent the general acceptance of Steiger's views, the excess of myopes with eyes showing myopic fundus change and the excess of refractions approaching emmetropia (Sorsby 1938).

It is not likely that further progress will be made by utilising routine clinical data for such investigations because of the statistical difficulties of such selected material (Sorsby 1937). It seems possible that the routine refraction under atropin, of children admitted to a fever hospital might provide a valuable curve which would have a statistical value. For this purpose the Wright Thomson skiascope would

Table II .

	Observer	Wibaut	Sorsby	B.of E.	Wibaut	Scheerer	Brown	Riddell
	Material	New Born	4-8 Years	4-15 Years	Adolescent	Adult	Adult	Adult
	Number	2398	672	2626	2920	12000	4431	704
	Dioptres							
+	6 etc.	4.6	0.9	2.2	--	--	1.0	4.6
	5	7.2	2.3	4.7	--	0.3	2.0	3.0
	4	12.8	9.5	13.7	0.2	0.7	4.7	4.1
	3	15.7	26.7	26.2	1.0	3.4	6.7	12.0
	2	27.5	33.5	26.0	6.4	14.1	17.0	23.5
+	1	29.8	19.0	15.1	23.3	28.3	19.0	29.3
	E.	1.9	5.7	6.8	31.7	33.0	25.8	9.2
−	1	0.3	1.6	2.9	20.3	8.4	11.9	4.1
	2	0.2	0.4	1.2	9.5	1.5	8.0	3.1
	3	--	0.3	0.6	4.1	0.2	2.1	0.9
	4	--	0.1	0.3	1.8	0.1	1.3	1.2
−	5 etc	--	--	0.3	1.7	"	0.5	5.0
		100.0	100.0	100.0	100.0	100.0	100.0	100.0

(B.of E. - Board of Education)

be a suitable method to use and this object was in mind when I established its accuracy.

If we assume that refractive errors are controlled by two corresponding factors, one dominant (H) and one recessive (m) present in the two members of a pair of chromosomes,a geneticist would describe them as alternative factors or allelomorphs. If hypermetropia is controlled by such an allelomorphic pair of genes HH whose members are carried in a pair of homologous chromosomes and myopia is controlled by the alternative phase mm of the same genes, the diagram (Fig. 2) may be constructed. This assumption is too simple to account for the distribution of refractive errors, but it may be used for illustrative purposes.

The members of each pair will segregate in the separating chromosomes during the formation of gametes. Thus HH individuals mated with similarly constituted persons could only have hypermetropic children. Similarly mm individuals could only produce myopic children. Such unions are called homozygous and the individuals forming such unions would be called homozygous individuals.

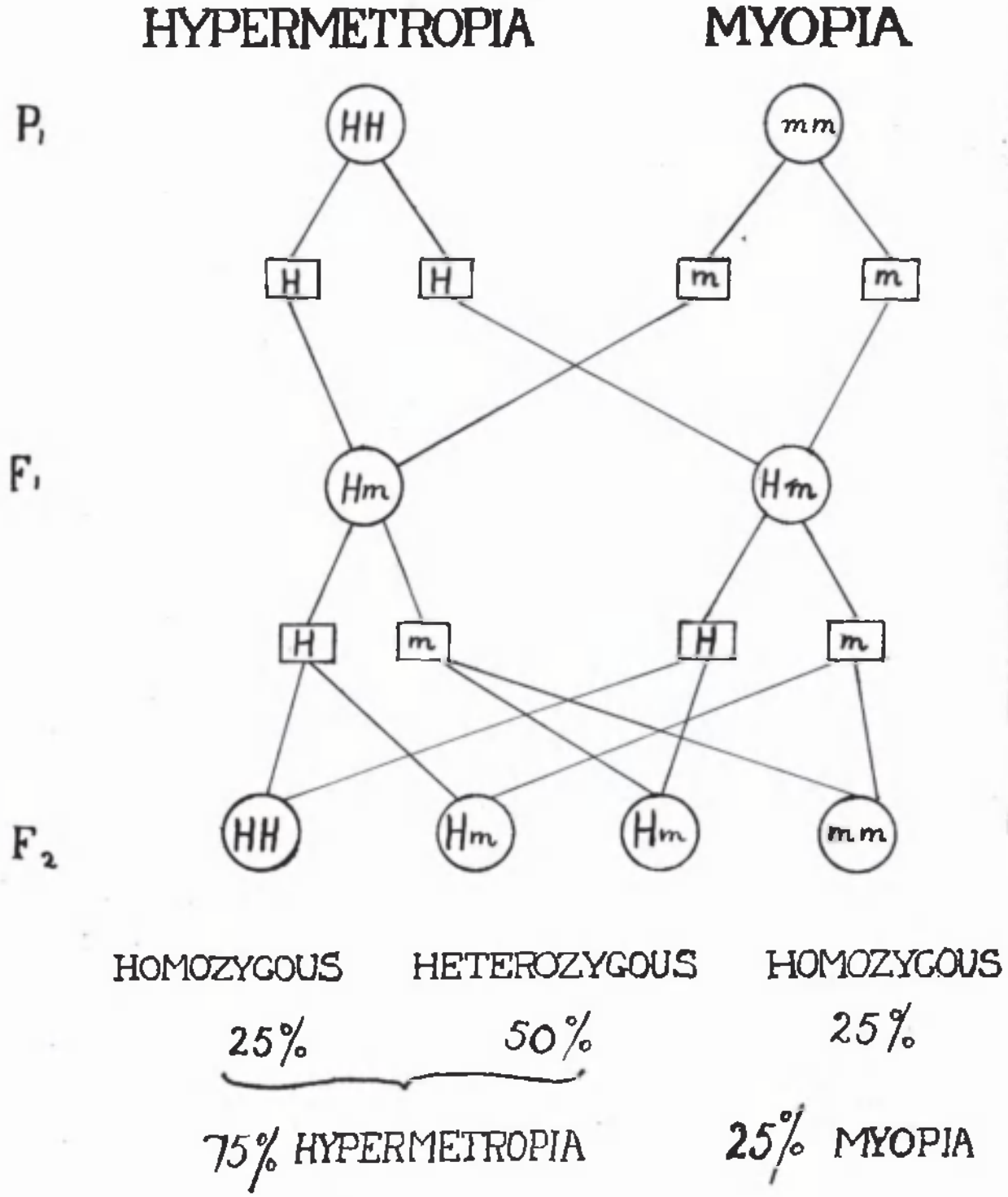
If an HH individual marries an mm, then heterozygous or mixed individuals will arise. In such a case

the members of a given pair of genes are dissimilar. It is a convention to describe the dominant member of such pairs with a capital letter and the recessive one with a lower case letter. A dominant factor is one which is fully expressed both in the homozygous and heterozygous form. A recessive only appears when the genes producing it are homozygous; its presence in the heterozygous form is masked.

Thus it follows that at present in human communities it is not possible to tell by clinical methods whether an individual is homozygous or heterozygous for a dominant condition. If the recessive alternative is wide spread in the community we may assume that the majority of parents are heterozygous. This problem does not arise in plants or in animals to the same extent, because it is possible to back-cross to the parent stock and so identify the heterozygotes.

The character developed by a zygote is its phenotype, whilst its actual constitution is called its genotype. Thus in the illustration, two zygotes HH and Hm will both manifest the dominant factor of hypermetropia and although they would be phenotypically similar the genotypes would be different. In the case of homozygotes, whether dominant or recessive the

FIGURE 2.


HYPERMETROPIA
MYOPIA
P1
HH
mm
H
H
m
m
F1
Hm
Hm
H
m
H
m
F2
HH
Hm
Hm
mm
HOMOZYGOUS
HETEROZYGOUS
HOMOZYGOUS
25%
50%
25%
75% HYPERMETROPIA
25% MYOPIA

phenotype and genotype are the same. In the diagram the F.2 generation show a phenotype ratio of 3 : I and a genotype ratio of I : 2 : I .

The law of independent assortment asserted that the segregation of any one pair of allelomorphs was independent of the segregation of any other pair and that the ratios arising from the assortment of such pairs could be predicted. If two sets of characters segregated separately in a 3 : I ratio, in combination the resulting ratio would be 9 : 3 : 3 : I . This law is not universally true because only those allelomorphs which are situated on different pairs of chromosomes can segregate independently. In man there are twenty four pairs of chromosomes and each must carry many allelomorphic pairs. Such pairs will tend to segregate together "because they are travelling on the same vehicle and may consequently be expected to reach the same destination" (Ford 1938).

"We now have to admit that all analysis of populations which take into consideration the inborn differences of individuals depend for their rigour on statistical treatment. This is true whether the analysis is

carried out on the progenies of mendelian breeding or of darwinian selection; for the study of uncontrolled human heredity it is the key to the whole problem". (Darlington 1939).

Complicated statistical methods were not employed by Gregor Mendel in his classical experiments, but after the re-discovery of his work at the beginning of this century they were found to be essential to progress. At first investigations were concerned with the significance of departures from expected ratios in the breeding of plants and animals.

When linkage relationships were discovered a more elaborate treatment became necessary. Modern mendelian theory is a particulate one in which hereditary factors are transmitted by genes. These genes are carried in the chromosomes, and the simile in common use is that the genes may be compared to individual beads upon a string. Certain portions of such strings tend to stick together and be transmitted together. Such portions may form a linkage group and factors transmitted together are said to be linked. A factor at one end of a string has less chance of being transmitted along with one in the middle, consequently at the reduction division of the chromosomes which preceded the formation of gametes, two such factors may be transmitted to one or other gamete by equal chance. If two factors are

close together, independent transmission is not a matter of equal chance ; there is a probability that they may stick together. They are then said to be linked and the degree of linkage may be given a statistical value.

An example taken from "The Study of Heredity" by E.B.Ford illustrates this point. "In the sweet-pea, purple flower colour is dominant to red, and erect flower shape is dominant to hooded. If we cross a purple and erect flowered sweet-pea,heterozygous for both pairs of genes concerned, with a double recessive plant (having red flowers of a hooded shape), we obtain four types in the F2 generation so produced. About 99 per cent. of the offspring are composed of the two parental classes in equal numbers, and about I per cent. are made up of the two recombinations between them, also in equal numbers. Since the four types are not in equality, those representing an interchange being very rare, it is clear that the genes controlling these characters are carried in the same pair of chromosomes. The existence,however, of a few red erect flowers and in equal numbers, of hooded purple ones, shows that an occasional transference of material has taken place

between the products of the homologous chromosomes, allowing about one per cent. of crossing-over. We express this fact by saying that there is a 'cross-over value' of one between the genes in question".

If myopia was controlled by a single recessive gene then the ratios indicated in Fig. 2 would be the expected ones and would fit in with Cohn's figures. There are many objections to this simple view. Myopia is not evenly distributed throughout the world and different populations show different degrees ;the cornea, lens and axial length of the eye are three variables which alter its dioptric power ; myopia may develop in diabetics and in elderly people from changes in the lens and without evidence of other change ; high degrees of myopia may exist without fundus change and with good central vision ; low degrees of myopia are found with marked myopic change ; typical 'myopic crescents' may be seen occasionally in hypermetropic eyes ; certain pedigrees may exhibit varying degrees of 'malignant myopia' and so on. Thus it follows that the problem of the inheritance of myopia is an extremely complex one and cannot be covered by any simple generalisation.

Although the diagram (Fig. 2) is too simple to explain the matter it has a value if we assume the existence of a linkage group in place of a simple

dominant-recessive single gene substitution. These speculations illustrate the important possibilities of linkage studies.

Pedigrees A and B show the inheritance of myopia and are of a type frequently seen in any ophthalmic clinic. Pedigree A shows an aparently 'dominant' transmission of a high degree of myopia. The patients examined varied between - 10.0 and - 16.0 D.

II.3 ,III.6 and IV.8 were not examined but the inheritance from III.2 to V.1 and 2 of a high degree of myopia with good central vision was confirmed. Such a pedigree is of course not incompatible with the view that all the factors concerned in the inheritance of myopia are recessive ones. If III. 1 and IV.3 are assumed to be heterozygous individuals no further assumptions need be made and the pedigree is in keeping with the view that myopia is controlled by recessive factors.

Pedigree B contains only one affected individual with myopia of - 11.0 Rt. and Lt. with excellent central vision. His father and mother are emmetropic and no other member of the family is known to be affected. This family is in good social circumstances and the boy is in perfect health. The myopia was first observed at the age of eight and he was twelve years

of age when he came under my observation two years ago. The myopia has not progressed so far. In such a case as this the parents are assumed to be heterozygous for the factor or factors concerned. His sister has a low degree of hypermetropic astigmatism.

A possibility regarding the occurrence of grave myopia is derived from a suggestion made by Grüneberg (1938) in another connection, that"normal overlaps" may occur. In the case of myopia this would imply that the primary effect of the gene substitution is not the clinical appearance of myopia and that it might not appear as such in portions of a pedigree. This is explained further in relation to retinitis pigmentosa.

It has been stated that uncomplicated myopia may occur as a sex-linked condition, but this must be very rare and according to Waardenburg (1932) requires confirmation. Sex-linked myopia associated with night blindness is extremely rare but is well established I have had the good fortune to be acquainted with members of one such family (Pedigree F).

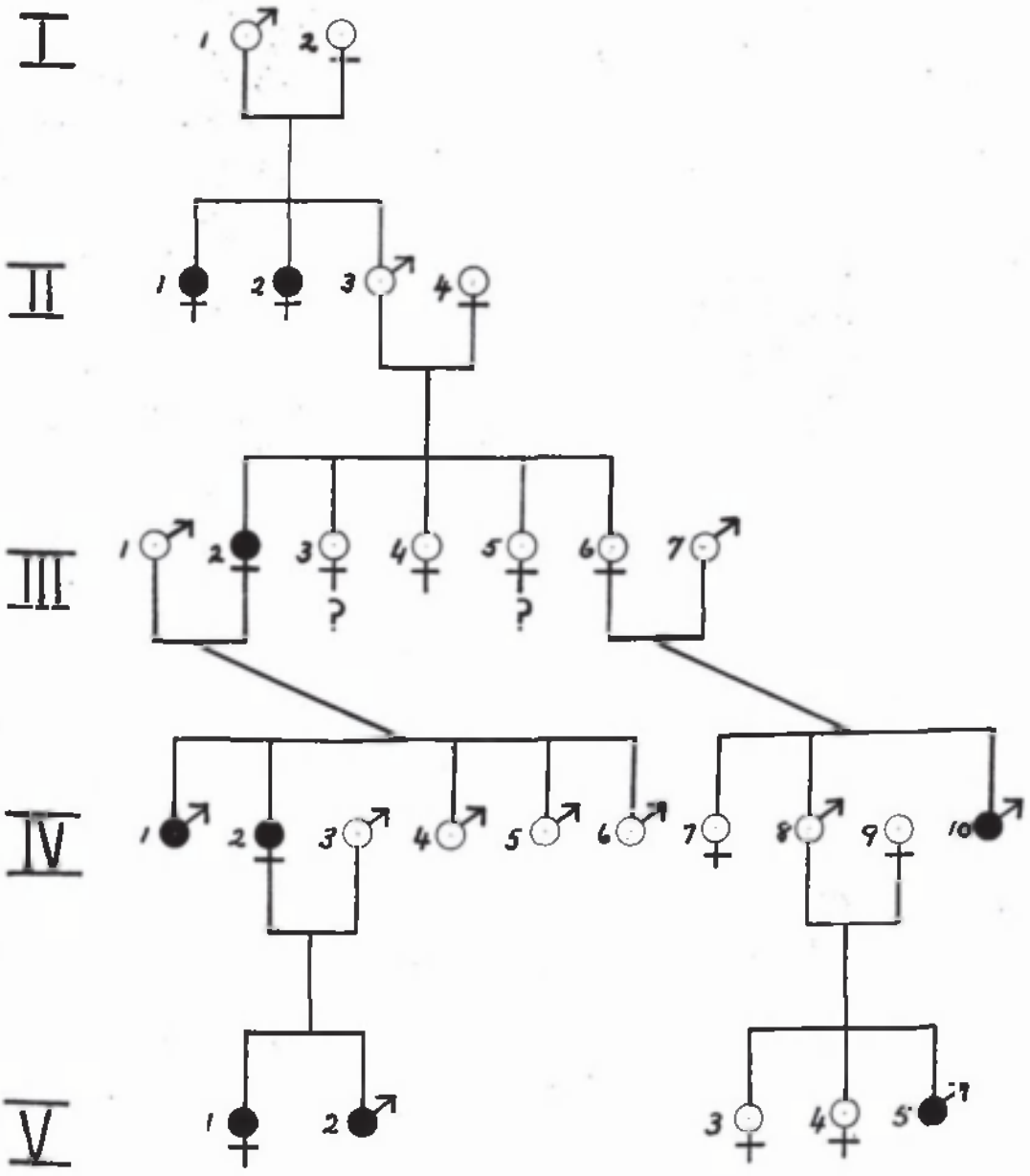
There is little doubt that several hereditary factors must be involved in the inheritance of refractive errors (if they are 'errors' at all) and the problem is to sort them out. The study of pedigrees is an

essential contribution to the solution of these problems.

The pendulum has swung between the extreme views of Cohn and of Steiger, between nature and nurture, heredity and environment, but the sentence with which Cohn ended his book is still apposite. "Let the saying of Donders never be forgotten ; 'Every case of progressive myopia is ominous of evil for the future'."

CHART A

MYOPIA



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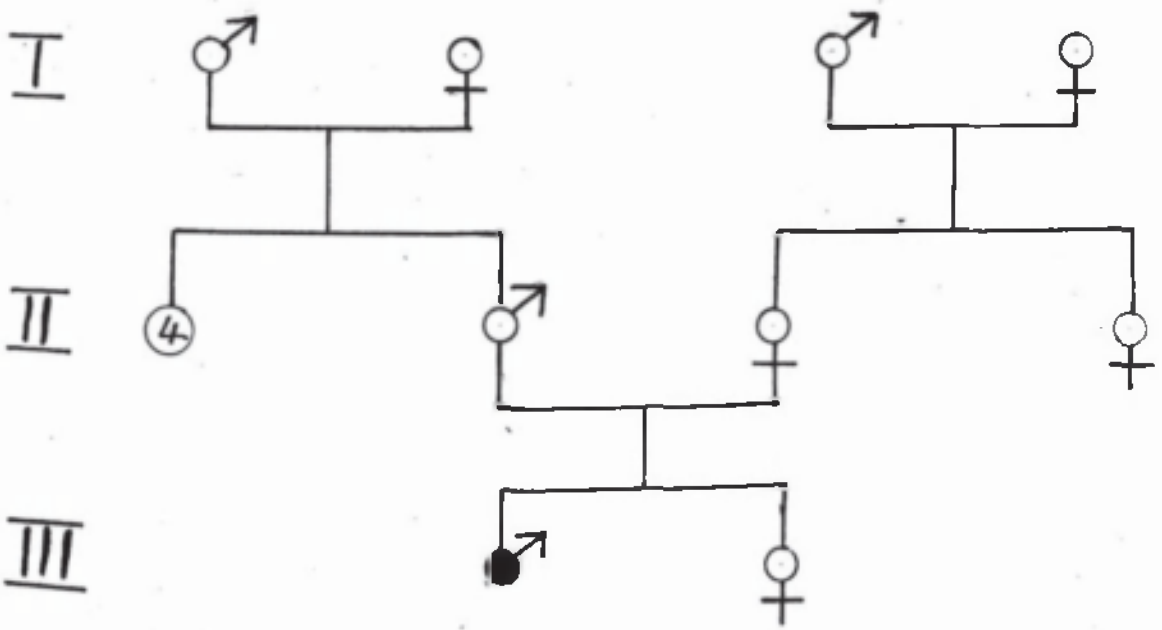
MYOPIA CHART B



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Section 2.

Congenital Stationary Night Blindness.

This condition is an extremely rare one, and only thirty-three pedigrees were found in the literature by Dr. Julia Bell (1933). The families may be divided into two groups; one in which both sexes are affected, and the defect may be transmitted by affected members of either sex, or in some cases by normal members. In the second group the condition affects males only, and is transmitted by unaffected females. In addition, the affected males in the second group are frequently myopic.

This rare defect has aroused world-wide interest owing to the fact that the largest human pedigree of any pathological condition is that of Jean Nougaret, a baker in the parish of Vendemian in the south of France, who was born about 1637, three hundred years ago, and suffered from it. The pedigree was first published in 1838 by Cunier; seventy years later the history was brought up to date by Prof. Truc and M. L'Abbe Capion, curé of Vendemian, at the instigation of Edward Nettleship who examined some of the cases himself, and re-published the greatly enlarged pedigree in 1907. At that date about two thousand

descendants were known and one-hundred-and-thirty-five were night blind. The inheritance was always direct, and an unaffected member never handed on the condition to a later generation. There are great difficulties in the way of investigating the pedigree further because the family are peasants, their speech is a dialect, and some are reluctant to admit the defect.

One example of each type of hereditary stationary night blindness has come under my observation. Pedigree C is one in which the transmission is dominant and not sex-linked. No myopia has been found in the members examined. No pathological change is seen in the fundus of such patients, and the investigation still depends to a large extent on the family history which must be taken with the greatest care. The example of hereditary stationary night blindness associated with myopia, and showing sex-linkage is discussed in Section 4.

The degree of severity varies in different accounts and it is quite possible that the defect is a graduated one. I have attempted to examine such patients in varying degrees of illumination, using standard candles at various distances, but the result was equivocal. This problem of assessing the degree of night blindness is one of some importance for two reasons.

In the first place night blindness may arise from a lack of Vitamin A in the diet or an inability to utilise it. This fact is now well known and has been exploited commercially. Various instruments are on the market which are supposed to detect differences in dark adaptation, but it is doubtful if sufficient accurate knowledge exists regarding the normal range of variation. I have been on the look out for such cases for eight years and only one case of night blindness has been seen (Riddell 1933). In that case the boy was brought to see me by his father, because it was observed that the patient could not see his clothes on a dark winter morning and did not see at a picture house, although his brother could do so. The other affected individuals whom I have seen were either members of Pedigree C or suffered from retinitis pigmentosa. In my opinion it is of great importance to have the history volunteered. To ask a group of under-nourished children if they can see in the dark is not likely to produce reliable answers. A trained ophthalmic surgeon may have difficulties in this matter and when he depends upon a medical interpreter, as happened in the investigation carried out by Pillat on xerosis conjunctivae, the results must be accepted with great reserve. In this investigation 209 Chinese soldiers were examined and 70 of them complained of night blindness.

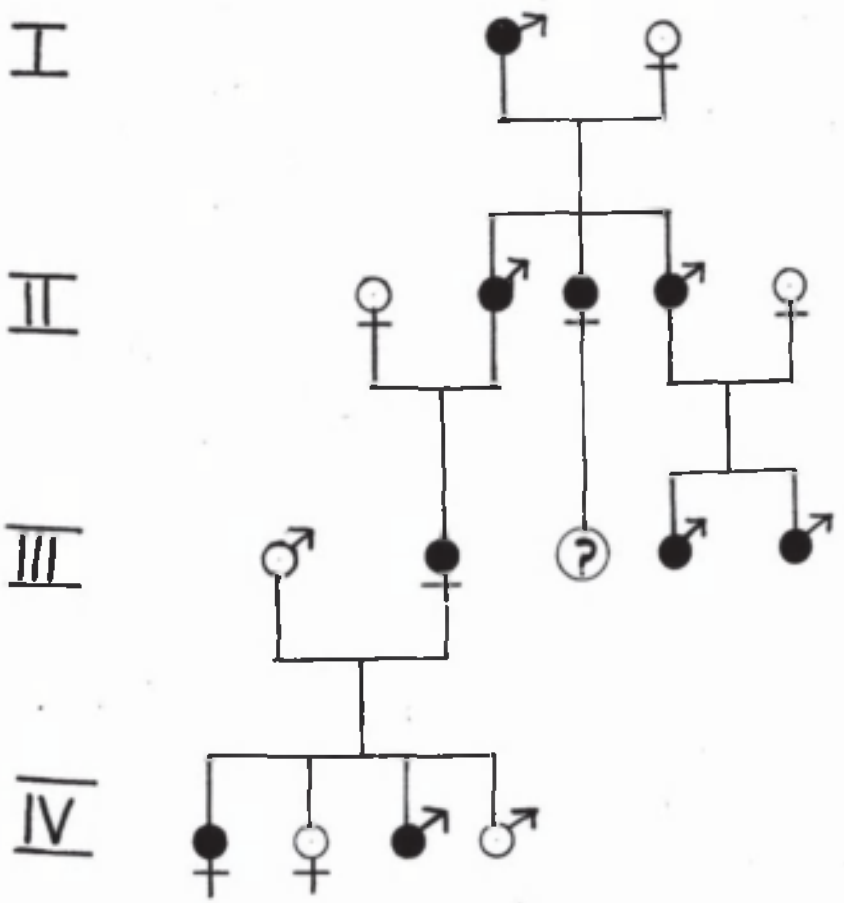
In the second place, night blindness is of importance in relation to military service. Hector Gavin writing in 1843, pointed out "that attention must be paid to the character, habits and conduct of the individual..... Night blindness is a common disease in Egypt, and was frequently feigned by our soldiers in the expedition under Abercrombie," and "From the returns in the Rangoon war, in 1824-5-6, it appears that nyctalopia was very common. And although it really existed in a great number, still many succeeded in feigning it". Millais Culpin (1933) pointed out that if night blindness occurred in the past as a military occupational neurosis it ought to have appeared in the Great War, but our literature is almost silent about it, continental literature, on the other hand, contained about forty references on the subject during that period.

Katherine Tansley (1939) criticises the greater part of the work done on the relation between vitamin deficiency and night blindness, very severely. She considers that the deplorable state of affairs seems to be due to the sudden incursion of clinicians and vitamin workers into the highly specialised field of subjective visual research. I agree with this view of the matter with regard to the nutritional cases. The hereditary ones are in a different category entirely, because there

is a family tradition in the matter which an experienced investigator can rely upon. It is hoped that further examination of members of Pedigree C may be undertaken.

CHART C

HEREDITARY STATIONARY NIGHT-BLINDNESS



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Section 3.

Retinitis Pigmentosa.

Recent work has suggested that Retinitis Pigmentosa is better regarded as a symptom than as an entity in itself. This was suspected even in pre-ophthalmoscopic times, before the name was given to the condition by Donders. Mackenzie (1835) wrote in the second edition of his text book that "on dissecting the eye of a deaf and dumb person, congenitally affected with night blindness, numerous black spots were found in the substance of the retina. In some cases there is reason to suspect that the proximate cause does not affect the eye, but the brain". This passage does not appear in the first edition of his book which was published in 1830. Eighteen years later, in 1853, retinitis pigmentosa was seen with the ophthalmoscope by van Trigt at Donders' clinic in Utrecht. The association of retinitis pigmentosa and deafness in certain pedigrees appears to be a close one. The occasional presence of polydactyly in such families has aroused much interest, but it was only present in five pedigrees in the series of two hundred and ninety seven included in the Nettleship Memorial Volume. There are a number of reports concerning isolated cases. Haldane

(1936) has shown that in certain families retinitis pigmentosa is partially sex-linked.

In 1938 Bourne, Campbell and Tansley described a pigmentary degeneration of the retina which was found in a mixed rat colony belonging to Messrs. Bemax Ltd. The condition was associated with cataract. The first change in the retina was the death of the cells of the outer nuclear layer (the rod nuclei) and this was seen at about three weeks of age. The rods disintegrated and the visual purple disappeared. By twelve weeks of age the whole of the outer nuclear and rod layers had disappeared and were replaced by a network of glial fibres. At this stage changes in the pigment epithelium became apparent. It became adherent to the retina and in pigmented eyes, pigment granules from the pigment epithelium migrated into the retina along the path made by the bundles of connective tissue and glial fibres. The pathological changes occurring in the retinae of these rats bear a striking resemblance to the changes which are described in retinitis pigmentosa. Treacher Collins (1919) held that retinitis pigmentosa was due to an "abiotrophy" of the retina and this rat pedigree gives some support to that view.

The first changes in the lens were seen during the second month of life, but cataract did not develop definitely in most of the animals until the third month.

The condition tended to be symmetrical, but differences in the intensity between the two sides were common. Major asymmetries in which one eye was heavily affected and the other eye entirely free did occur, but were rare. About 40% did not show any sign of cataract, but some of these showed changes in the lens shagreen, and others a persistent hyaloid artery.

A histological study of the eyes showed that all homozygotes whether they showed cataract, shagreen or persistent hyaloid artery, or whether they were normal ophthalmoscopically, exhibited the very characteristic changes in the retina under the microscope. They all showed the retinal degeneration. On the other hand, not a single individual was found who combined cataract, shagreen, or the hyaloid artery with a normal retina. In the opinion of Bourne and Grüneberg (1939) there was no doubt that the primary hereditary factor brought about the retinal changes and that the other anomalies were secondary. The pathological mechanism between the primary and secondary effects are not clearly understood. Apart from the eye anomalies, no pathological conditions were seen in the animals. In particular a rough test showed that the sense of hearing was not impaired.

The inheritance of the syndrome was found to be simple. An affected male, with degenerate retina and cataract, was out-crossed to an unaffected female. Sixteen

F.I (First Hybrid Generation) individuals were normal ophthalmoscopically and histologically. Therefore the condition behaved as a recessive one. F.I. females back-crossed to their affected father produced twenty two offspring. Eleven of these developed lens changes and one only showed a hyaloid remnant in one eye ; they all had degenerate retinae . This is a very good approximation to the expected I : I ratio from such a back-cross.

Hereditary factors producing cataract are quite common in mammals and are of course well known in man. Cases have been described of pedigrees in horses, cattle, dogs of various breeds, rabbits, rats and mice. In some the inheritance is dominant in others it is recessive, but the groups tend to be rather mixed.

Retinitis pigmentosa has been described in dogs without the occurrence of cataract by Magnussen (1911) and in mice by Cohrs (1933). There is also a curious condition of rodless retina described in the mouse by Keeler (1927) but it differs fundamentally from the rats described by Bourne because the rodlessness was

produced by an arrest of development, whereas im the rats the retina was at first fully differentiated and then underwent a degeneration of the rods and the outer nuclear layer. They consider the condition in the rats to be due to a recessive factor which causes degeneration of the retina at the age of three weeks, later in life some of the animals, but not all, develop changes in the lens which may lead to mature cataract. They hold that the cataract depends in some way upon the retinal degeneration and that the changes correspond closely to retinitis pigmentosa in man.

Further they are of the opinion that the principle is demonstrated that primary hereditary factor effects (in this case the retina) may show a straight-forward mode of inheritance, whereas the secondary effects may tend to exhibit irregularities of manifestation.

The principle is of very great clinical interest and importance. The literature of genetics shows many examples of individuals who according to their genetic constitution should show an abnormal condition but fail to do so. It is thought that such "normal overlaps" may be due to modifying factors or to environmental conditions.

An example of this occurs in acholuric jaundice in man where the normal overlaps are now known to show abnormality. The condition appears to be due to a

dominant factor with irregular manifestation in pedigrees based solely upon the fully developed anomaly. Careful investigation of the "normal" transmitters has shown that they invariably show a decreased resistance to haemolysis and a globular shape of their erythrocytes. Pedigrees investigated for these anomalies show a clear cut dominant transmission.

Thus if classification is based upon a secondary effect (the haemolysis) instead of on the primary defect (erythrocytes) irregular pedigrees are found. In view of such cases Grüneberg (1938) has suggested that irregularity in the manifestation of hereditary factors may be accounted for by this spurious behaviour. In other words the factor manifestation is always regular as regards its primary effect, and irregularities become apparent if the "characters" which are subject to mendelian analysis are in fact more or less remote consequences of the primary action.

The suggestion cannot be strictly proved but it becomes more likely with every case where the principle is shown to apply. This has been done in the case of acholuric jaundice in man and in the case of the rat pedigree referred to above.

During the past thirty years clinicians have become familiar with certain syndromes or grouped conditions which have received various names. An example is the Laurence-Moon-Biedl syndrome in which retinitis pigmentosa, polydactyly, hypogenitalism, mental deficiency and obesity occur together. In 1938 it was shown by Cunningham Dax that in retinitis pigmentosa, conditions of pituitary abnormality, or where the gland is subject to physiological stress, a melanophore dispersing substance is present in the blood and in the urine of such patients. When injected into frogs the melanophores were dispersed and in certain cases the frogs turned almost black. I confirmed this observation in a number of cases of retinitis pigmentosa (Riddell 1939b). The unaffected members of retinitis pigmentosa families and particularly the sibs of affected individuals should be investigated in this manner. If it were found that some of them showed the presence of a melanophore dispersing substance, it would follow that they were normal overlaps, and that the primary lesion might lie in in the pituitary. On the other hand, if the melanophore dispersing substance was found only in certain cases of retinitis pigmentosa then the pituitary abnormality would be secondary to the retinal condition.

In a recent paper on the Laurence-Moon-Biedl syndrome (Sorsby,A very and Cockayne 1939) the literature is reviewed and the authors point out the frequent occurence of one or more components of the syndrome in the ascendents of patients showing the full syndrome. No case of the inheritance of the full syndrome is known, though cases are reported indicating that patients exhibiting the syndrome are not sterile. They draw attention to a whole series of allied conditions which are classified into eleven groups.

With regard to its inheritance there are two main theories, the first is that one gene produces all the signs and that incompleteness of the syndrome is due to the action of modifying genes : the second is that the syndrome is determined by two or more genes. Franceschetti (1930) favoured the first view and Sorsby, Avery and Cockayne supported the second and suggested that "the syndrome is determined by two recessive genes in the same chromosome, or that it is dependent on some chromosome error such as dislocation or translocation".

It is my opinion that our knowledge has not advanced sufficiently far to justify the assumption that dislocation or translocation occurs. The possibility of making human chromosome maps was not demonstrated until Bernstein showed in 1931 the theoretical possibility of doing so and human linkage studies must be more advanced before any definite opinion can be formed in relation to these multiple syndromes.

Pedigree D.

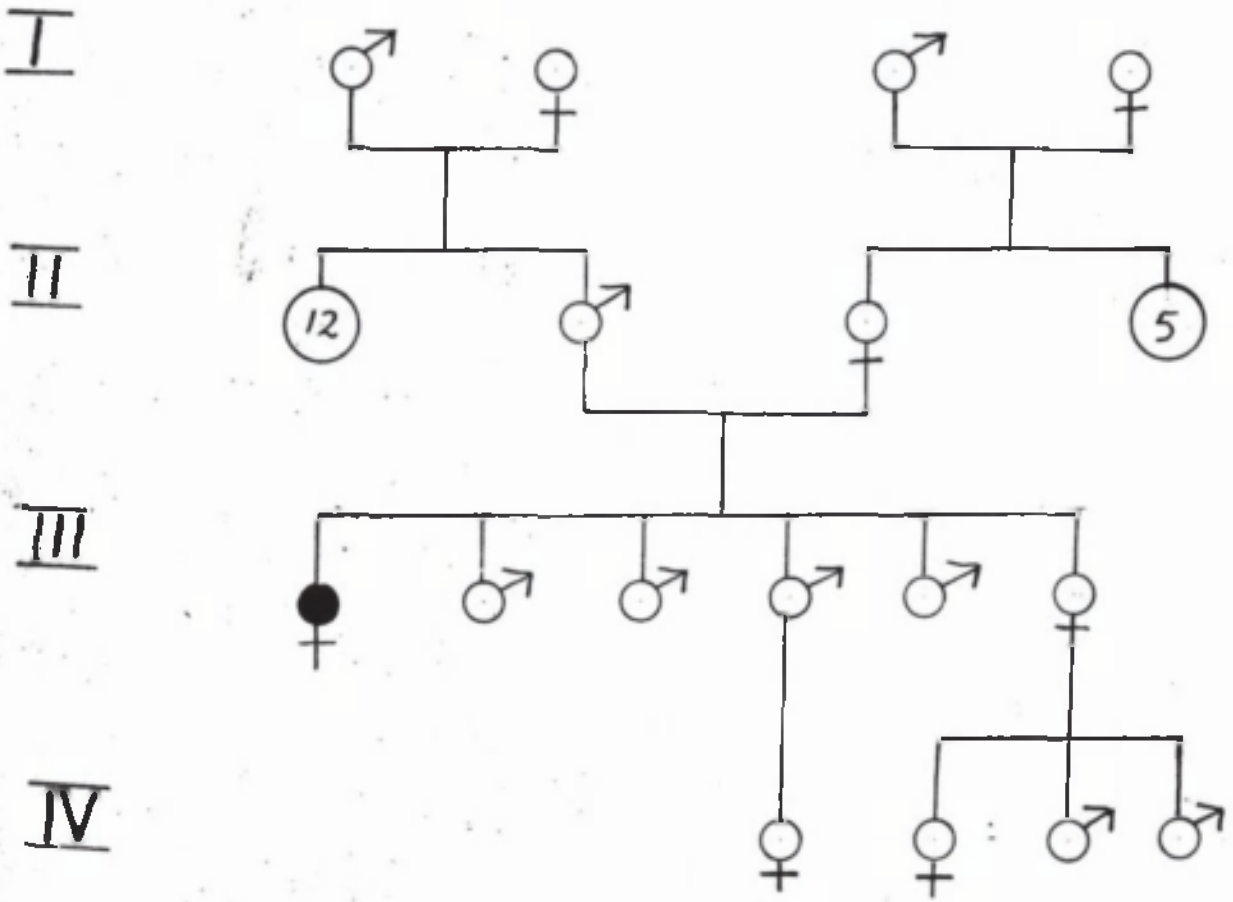
The first pedigree of retinitis pigmentosa contains only one affected individual, but she had a brother who was deaf. Her father had a sister who was "born with bad sight and very small eyes". Her mother did not "see too well at a distance" but could read easily. She was presumably myopic. This patient (III.1.) had a melanophore dispersing substance in her urine. Her relations all live in Fife and more details were not available. She is married but has no family. She was first seen by me when fifty-three years of age and she complained of defective vision in dull light. This had been present for eleven years. Her central vision with myopic correction was very good in both eyes (R.E. ♂ - 1.0 D.Sph. -2.0 D.Cyl. 90°.6/6. L.E. -1.5 D.Sph. -0.5 D.Cyl. 90°. 6/9 and J.1. unaided in both eyes). Her fields in good daylight were reduced to about 20° round the fixation point and in dull illumination this was reduced to less than 10°. Both fundi showed the typical changes associated with retinitis pigmentosa. There was a posterior polar opacity in the right lens, but the left one was clear.

With the test types illuminated with one standard candle at various distances and shaded from the patient :-

I candle at 4 m. patient read 4/60 -- myself 4/36
I candle at 2 m. .. .. .. 4/36 -- 4/12
I candle at 1 m. .. .. .. 4/24 -- 4/9

The patient was dark-adapted for half an hour before the test was carried out.

RETINITIS PIGMENTOSA CHART D



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Pedigree. E.

Retinitis Pigmentosa and Myopia.

Although only one member of this pedigree lives in the West of Scotland, I have obtained a considerable amount of information regarding it.

I.1. Died aet. 94; her granddaughter, III.7. reports that she did not wear glasses at all and could see to sew by candle-light. She was presumably myopic.

I.2. Husband of I.1.; no information was obtained.

II.1. William T. 1842 - 1910; was knocked over by a taxi-cab and killed, aet. 68.

II.2. Fanny J. 1843 - 1924; died aet. 84; is reported to have had wonderful sight, especially for long distances, by her daughter, III.7.; this sibship had eleven children.

III.1. Arthur T. 1866 - ; had an injury to the left eye in childhood and only requires to wear glasses for reading. He wrote to me about his children.

IV.1. Dorothy E. 1891 - ; reported to be long sighted; wears bifocal glasses.

V.1. John E. 1922 - ; son of IV.1.; wears glasses for long sight and has special exercises to correct the right eye which is amblyopic.

IV.3. Kathleen T. 1901 - ; has worn glasses since the age of 19, and is very short sighted.

III.3. Ernest T. 1867 - 1896; was not married and no more information was available.

III.4. Walter T. 1869 - ; is not married; he reports that he is short sighted and can read all sorts of printed matter without the use of glasses. He confirmed the statement that his father and mother, II.1. and 2. only wore glasses for reading and close work.

III.5. Edgar T. 1870 - ; married but has no family; he has got typical retinitis pigmentosa, and his correction is -5.0 D. Sph. Rt. and Lt. With glasses he reads 6/12 in either eye and small print unaided. The fields of vision are reduced to 10° around fixation point; his colour vision tested with Ishihara's Plates was normal. He has had difficulty in seeing in the dark for many years, and he was tested by means of standard candles in the following manner:-

With test types illuminated with candles burning at various distances and shaded from the patient's eyes:-

1 candle at 5m. patient could read -- Myself 6/60.
2 candles " 5m. " " " -- " 6/24.
3 " " 5m. " " " 6/60 " 6/18.
4 " " 5m. " " " 6/36 " 5/9.
4 " " 3m. " " " 6/36 " 6/9.
4 " " 1m. " " " 6/24 " 6/6.

In artificial light patient could read 6/18.
" good daylight " " " 6/12.

III.7. Laura McN. 1872 - ; was examined on my behalf by Dr. N.P.R. Galloway of Nottingham, who reported that she had no sign of retinitis pigmentosa, but that she was highly myopic; R.E. -9.0 D. Sph. L.E. -8.5 D. Sph. with which she read 6/6 in each eye.

IV.4. Daughter of III.7. is reported to have good vision, but suffers from asthma.

III.9. Elizabeth W. 1874 - ; has only worn glasses for reading and sewing, but her son IV.6. has got retinitis pigmentosa.

IV.6. Robert W. 1903 - ; was examined by Dr. Snowball of Burnleigh and the late Dr. Whitehead of Leeds, both of whom diagnosed retinitis pigmentosa. His

mother reports that as a child he was very awkward and walked into things such as lamp-posts. This was believed to be due to carelessness.

V.3. Pamela W. 1936 - ; is reported to be healthy.

III.11. Maud T. 1876 - 1881; no information.

III.12. Edith T. 1878; died aet. 3 months.

III.13. Linda C. 1879 - ; was examined by Mr. Rutledge of Norwich to whom I am indebted for the following information:- Her vision in the R.E. with -1.0 D. Cyl. Axis 35°. was 6/6, and in the L.E. with -1.0 D. Cyl. Axis 130°. was 6/6. Her fields of vision were contracted to about 30°. The fundi showed the usual pigmented changes, and the pigmentation extended towards the disc on the nasal side. The fields were contracted and the discs pale.

IV.9. Mary C. 1910 - ; reported to be healthy by her mother, III.13. She is married but has no family.

IV.11. Rex C. 1913 - ; was examined for me by Dr. N.P.R. Galloway of Nottingham, to whom I am indebted for the following information:- His vision R.E. and L.E. 6/12, with correction for hypermetropic astigmatism vision 6/5 in each eye. The fundi were perfectly normal and there was no night blindness.

III.15. Stanley T. 1880 - 1918: was killed in the Great War, and no other information available.

III.16. Frederick T. 1882 - ; reported that his eyes were examined by Sir A. Lawson in 1911 who corrected his short sight. In 1921 he was examined by Mr. Edridge Green who ordered, R.E. -1.5 D. Sph. with -1.5 D. Cyl. Axis 180. He reports that for the last six years he has done his office work without any glasses.

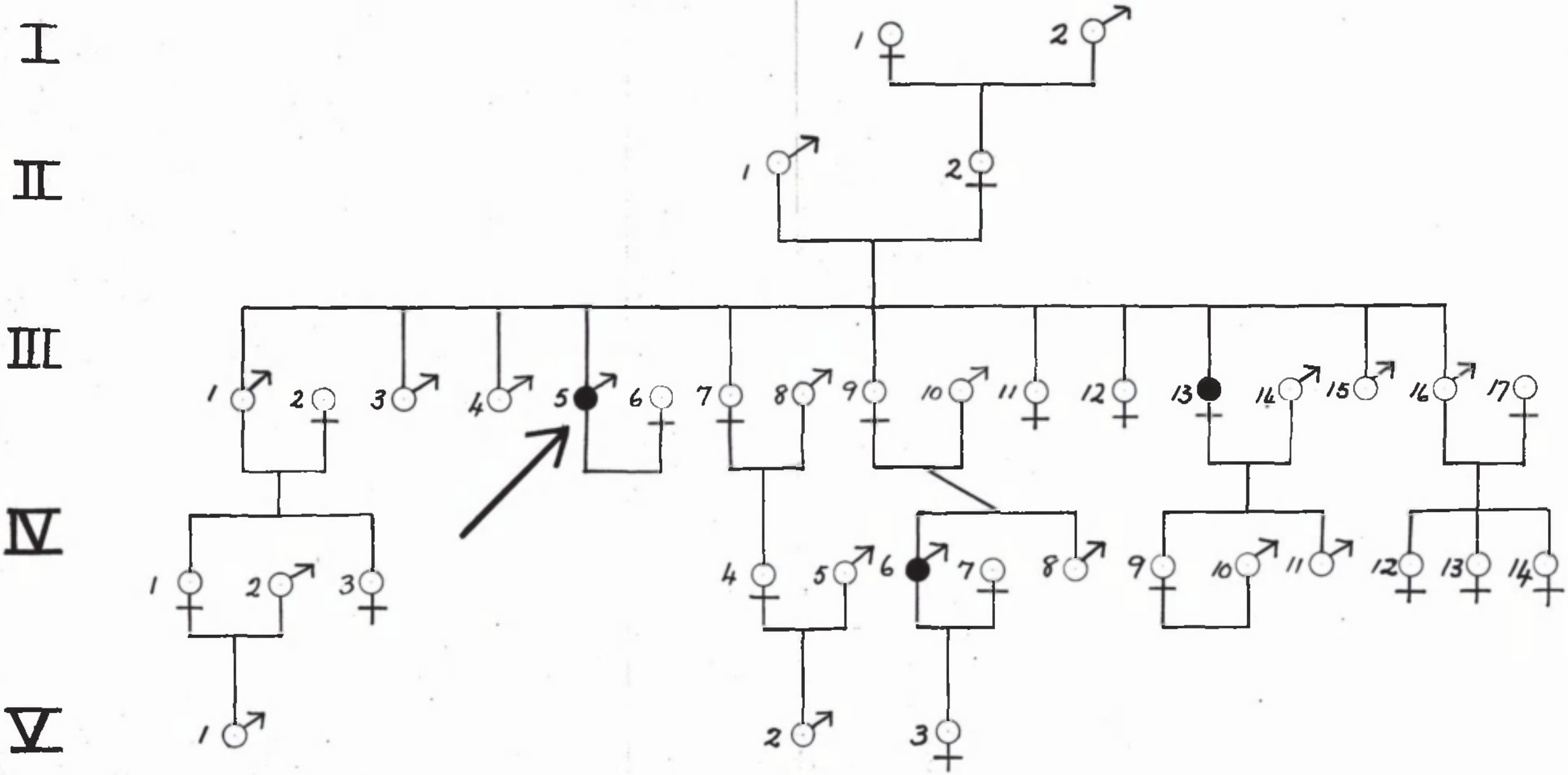
IV.12. Margaret T. 1914 - ; daughter of III.16. has got long sight and wears +0.5 D. Sph. Rt. and Lt.

IV.13. Eleanor T. 1918 - ; has got hypermetropic astigmatism and wears +0.75 D. Sph. with +0.5 Cyl. Axis 90.

IV.14. Jean T. 1919 - ; has got myopic astigmatism and wears R.E. -2.5 D. Sph. L.E. -0.25 Sph. with -0.75 D. Cyl. Axis 180.

RETINITIS PIGMENTOSA

CHART E



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Few hereditary diseases are now believed to be isolated conditions which have only local manifestations and as knowledge increases their number will diminish further. We do not know the cause of myopia, nor are we in a position to control it. It is known that certain changes in the eye are associated with it and that in certain cases we can establish a hereditary history of the same condition, such as detachment of the retina, choroidal changes or corneal astigmatism. Sorsby (1935) concluded "that the higher incidence of visual defect in Jewish children is to be explained not only by the onset of myopia in a larger group of potential myopes but also by the greater frequency of astigmatism. The greater incidence of astigmatism among Jews is perhaps to be explained along biological lines. Astigmatism is frequently inherited as a recessive manner and would be frequent in such a highly inbred people as the Jews".

It is certain that hereditary factors are concerned. They may be the same as those which control growth in other parts of the body or which control the formation of primative tissue destined to become a ductless gland. The whole problem of metabolic control arises and recent

workers all seem to be dissatisfied with the view that myopia is a purely ophthalmological problem attributable to excess of close work or other misuse of the eyes.

Hereditary stationary night-blindness, although a rarity, may furnish valuable information to other branches of knowledge than heredity and ophthalmology. It might be due for example to a defect in visual purple which in turn may be controlled by factors concerned in the utilisation of vitamin A. We do not know what would happen if an affected member of such a pedigree mated with a hight myope, although we do know that when night-blindness is sex-linked it is frequently associated with myopia. It is of interest that not all the members of such pedigrees affected with night-blindness are myopic. As it is very doubtful if myopia ever occurs as a sex-linked condition by itself, such cases may be regarded as 'normal overlaps' analogous to those found in pedigrees of acholuric jaundice referred to above.

There is of course no particular reason for the assumption so frequently made that myopia is always controlled by the same set of factors. It is well

known amongst animal geneticists that similar conditions may be determined by different genes. For example there are at least three kinds of white plumage in the domestic fowl. One has arisen as a dominant sex-linked mutation, one as a dominant mutation which is not sex-linked and a third appears to be recessive (Hogben 1939).

The questions raised by the discovery of a melanophore dispersing substance in the blood and urine of patients suffering from retinitis pigmentosa removes it from its isolation as a 'hereditary eye disease' and compels its reconsideration from a wider aspect. Its association with other conditions was lost sight of in the course of the somewhat arid controversy amongst ophthalmologists concerning its origin from a vascular or neural 'cause'.

The view that an inherited character or disease depends upon the action of a single gene acting in isolation can no longer be maintained. The action of a gene is complimentary to that of others, that is to say it reacts to its genetic environment, just as the organism as a whole reacts to the physical environment in which it finds itself.

This section may be concluded with the statement of some matters upon which further research may be based.

I. There is need for the construction of refraction curves from unselected samples of the population. As racial differences are known to exist it is important that such curves should be constructed for different communities. Figures applicable to American or Jewish populations should not be used where they may not be applicable.

2. A method of measuring the axial length of the living eye is at present a subject of research in this country (Sorsby 1937). One application of this knowledge would be to enable the three main dioptric components of the eye to be separated.

3. Once the dipptric power of the cornea, lens and the axial length of the living eye is known progress in our knowledge of the origin of refractive errors could be made. For example by the application of the formula $y = bx^{\alpha}$ (see appendix I.)

4. There is need for a simple clinical method for the estimation of dark adaptation and scotopic vision. A t present the normal variations are not known and investigation of hereditary and nutritional night-blindness is handicapped.

5. The suggestion made by Grüneberg concerning normal overlaps is one which should be kept in view in all clinical investigations of hereditary conditions.

6. As the concept of one 'cause' for one 'disease' is increasingly more difficult to maintain a more flexible approach to hereditary conditions appears to be necessary.

7. Co-operation between geneticists and clinical workers should be closer than has been the case in the past. It is now possible to apply refined statistical methods to problems arising in the study of small human pedigrees. The possibility of establishing genetic linkage increases the importance of clinical observations on human hereditary conditions.

Part two is concerned with the application of such methods to the study of haemophilia and colour-blindness.

Section 4.

Retinitis Pigmentosa, Choroideremia and Sex-linked Night Blindness with Myopia occurring in the same Pedigree - Chart F.

This section contains a brief account of a unique pedigree which was extensively investigated by Smith and Usher (1916). It has been brought up to date by Usher (1935) and by myself (1939b). III.7 was myopic and suffered from congenital stationary night blindness. His maternal uncle II.1. was similarly affected. III.7. married III.41. a woman who suffered from retinitis pigmentosa. They had four children and the eldest, IV.8. has got choroideremia. This man has been under observation for over thirty years and is now aged 49, is married but has no children. His wife is two years older than he is. Of his two sisters, one lives in Canada and has not been examined, but the other lives in this country and examination of her family is negative. Water colour drawings were made of the fundi in this case in 1914 and were reproduced in colour in the Nettleship Memorial Volume. At this time the vision of the right eye was 6/18 with -2.5 D. Sph. and -1.5 D. Cyl. axis 180°, and the field of vision was contracted to

within 10°. Night blindness was marked, but he was able to name red, yellow, green and blue with the spectroscope. The vision of the left eye with myopic correction was 6/24 and he was unable to see colours with it. Tests with coloured cards and wools were all unsatisfactory. In 1924 the vision in the right eye was 6/24 with -6.0 D. Sph. and -2.5 D. Cyl. axis 180°. It is now reduced to perception of light. The original drawings made in 1914 show a leash of blood vessels running out towards the macula. This has now disappeared. The condition of the anterior segment of the eye has not altered materially since the original description. He has still got only a few spots of opacity in the lens and fine floating opacities confined to the anterior part of the vitreous.

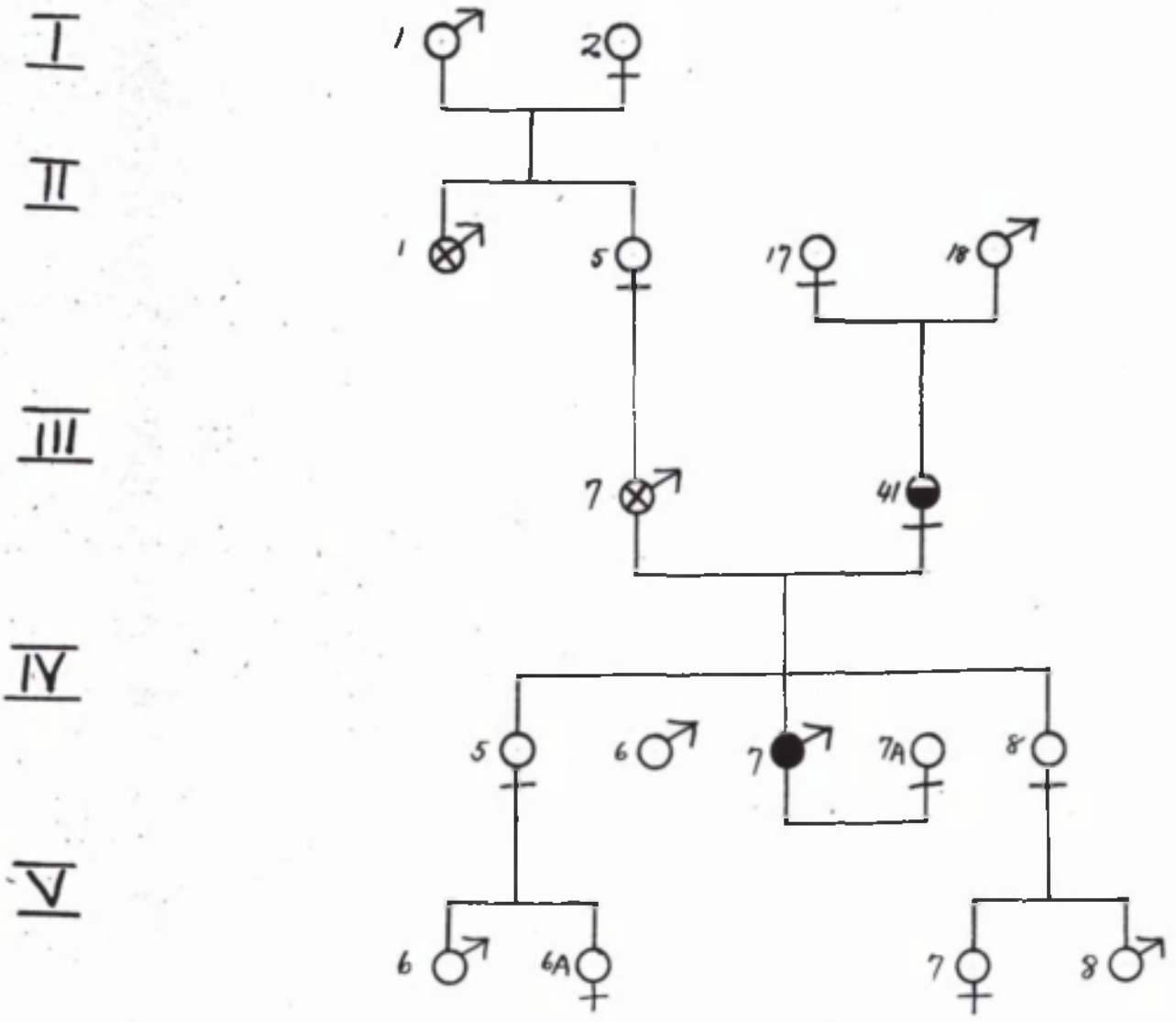
I have known this patient for thirty years. In his young days he was a butcher's message boy near my home, and managed to do this in spite of the constriction in his fields. Later he was trained as a boot-repairer and worked in the Blind Asylum.

In an attempt to find a melanophore dispersing substance in his urine six frogs were chosen, three pairs of similar size and colour. Three were injected with urine from a normal patient and three from the choroideremia patient. No colour changes

were seen. A control experiment was carried out with five pairs of matched frogs and urine from patients with retinitis pigmentosa. Colour changes occurred in four frogs out of the five. The samples were prepared in the manner described by Dax and 1.0 cc. of urine was used. The reaction was well seen in the retinitis pigmentosa frogs. In these investigations I was assisted by Dr. F. J. Hebbert, the House Surgeon at the Ophthalmic Institution in Glasgow.

There are two views regarding the origin of choroideremia. It may be a congenital absence of the choroid. On the other hand, Dr. Bedell (1937) considers that "as it develops during the life of the patient it must not be considered as a congenital absence of the choroid, but as a dissolution of that membrane". Usher (1935) pointed out that it was curious that none of the cases reported at the time of the first examination was younger than fourteen years, and he doubted if all the cases formed a homogeneous group. The age of onset does not affect the possibility of heredity being an important factor in its production. In conversation Dr. Bedell told me of a professional base-ball player in America who suffered from typical choroideremia. Obviously such a case shows that the condition may develop during the life of the affected individual.

CHART F



⊗ NIGHTBLINDNESS AND MYOPIA

◒ RETINITIS PIGMENTOSA

● CHOROIDEREMIA

ABRIDGED CHART

Sex-linkage and Mutation.

As a preface to the consideration of the next section this note on sex-linkage and mutation is interpolated.

In man sex is controlled by a pair of chromosomes called X-chromosomes, both of which are present in the female and one passes into every gamete. The male has got only one X-chromosome and its partner is the Y-chromosome. Either X or Y passes into the gamete but not both. The sex of the offspring consequently depends upon the male gamete. It is usually taught that the Y-chromosome carries very few genes and that it does not control sex.

The female receives one X-chromosome from her father and one from her mother. The male receives one X-chromosome from his mother and the Y-chromosome from his father. It is not the type of chromosome which determines the sex of an individual, it is the number of genes carried on the X-chromosome. A double supply causes female development, a single supply a male.

Genes are carried on the X-chromosomes which have nothing to do with the determination of sex. Colour-

blindness and haemophilia are two examples of this. Colour-blindness is a recessive condition which appears in the male because there is not a normal counterpart present,as there is in the second X-chromosome of the female. If a woman had a colouredefective father and a mother who was heterozygous for the defect, she might be colour-blind. Hence colour-blindness in women is relatively uncommon.

Haemophilia is transmitted in a similar way and theoretically haemophilic women may occur. They do not do so. There are seven pedigrees of the type (R Y × RR) on record and the affected offspring are exclusively male (Hogben 1939). There were 25 children arising from such matings and 14 were normal females and 11 affected males. It is possible that the gene in duplicate is lethal and consequently the zygotes do not develop, or that in duplicate the genes cannot become manifest owing to other factors in the environment of the female soma. Attempts have been made to treat haemophilia with ovarian tissues and extracts but the results are equivocal.

The X X and X Y mechanism determines whether male or female sex glands will develop ; the secondary sexual characteristics are not directly controlled by it.

Recombination of various factors may alter the hereditary constitution of a pedigree. A good example is shown in the careful investigation of the ascendents of patients suffering from the Laurence-Moon-Beídl syndrome already referred to. The choroideremia pedigree (Chart F) is a second example. Such changes may arise through genes crossing over from one chromosome to another. The association of sex-linked night blindness and myopia could arise in this manner.

Changes may also occur through a process called mutation. Genes may exist in a number of different states and pairs of allelomorphs may be made up of similar or dissimilar members. When a gene passes from one state to another the process is called mutation. We do not know the cause in nature, but it can be produced artificially by means of X-rays. This is not a destructive process, because in some instances the reverse process has been induced by the same means. This work was initiated by H.J.Muller in 1927 when he showed that the mutation rate in Drosophila could be increased about 150 times by exposure to X-Rays.

Some parts of a chromosome are mofe liable to change or mutate than others, and in Drosophila mutation rates can be calculated. In nature such changes are rare, between one chromosome in a million and one in ten million in every generation. The highest mutation rate known for any locus in Drosophila Melanogaster is I in 300,000 (Ford). This occurs in the series of multiple allelomorphs which produce eye colours, which range from a red shade to white.

Mutations may occur in body cells as well as in gametes. An excellent example is heterochromia iridis which is frequently seen in ophthalmic clinics.

"How often, when a new phenomenon has been observed, do we hear the question asked ; What is the cause of it ? A question which it may be absolutely impossible to answer, whereas the question ; To what degree are other phenomena associated with it ? may admit of an easy solution, and result in invaluable knowledge".

Karl Pearson (1857-1936).

Part II.

Haemophilia and Colour-blindness.

In 1936 I was asked to examine haemophilic pedigrees for colour defective individuals on behalf of Dr.Julia Bell and Prof. J.B.S.Haldane. Seven haemophilic pedigrees were investigated and the affected members were examined for colour defects. Of these two were found to contain colour defective individuals and they were worked out as fully as possible. Both pedigrees have been published separately (Riddell 1937 and 1938) and are included in this thesis as Pedigree Charts G and H.

Ishihara's isochromatic plates 4th. Edition were used in all cases and positive findings were confirmed with Ishihara 7th. Edition, Stilling's plates, the Edridge-Green lantern, bead and wool tests. In certain cases it was not found possible to use all methods, but no case was accepted without confirmation of some sort. Superficially it might be thought that dental clinics would be a suitable place to find records of haemophilics, but although many cases were obtained from dental school clinics, only one proved to be a genuine haemophilic.

Pedigree G was included in a paper on the linkage between the genes for colour-blindness and haemophilia in man published by Bell and Haldane in 1937. This section is entirely based upon their work. It is generally accepted that the genes for haemophilia and for colour-blindness manifest themselves in all males who carry them. As already pointed out haemophilic women are unknown or at least extremely doubtful. One such pedigree was published a few years ago from the West of Scotland containing two alleged haemophilic women. I re-investigated this pedigree and satisfied myself that the women in question were not haemophilics. They had not been examined by the original recorders; neither had any haemorrhages into joints, one had severe haemorrhage following the extraction of teeth and the other had had a serious post-partum haemorrhage. I interviewed both of them, as well as their male haemophilic relatives. As the pedigree contained no colour-defective members it has not been re-published.

According to Waaler (1927) the genes which determine 'protanopia' and 'deuteranopia' form a series of five allelomorphic genes with the normal gene. Haldane(1935) suggested that there are at least two different allelomorphic genes for haemophilia.

It was of considerable importance to demonstrate that the principals of linkage which have been worked out for other animals also held good for man and this investigation by Bell and Haldane was the first in which linkage was measured in man.

Colour-blindness was chosen because it is relatively common and haemophilia, although rare, because it could have no effect upon the detection of colour defects. Bell and Haldane found two such pedigrees in London, Dr.C.L.Birch of Chicago provided another, Dr.Madlener of Kempten(Germany) contributed further information concerning a family which he published in 1928 and in which the first evidence of linkage between the two genes was obtained, a pedigree published by Davenport (1930) and my own contribution (Chart G) completed the series of six upon which the investigation was based.

It was pointed out by Haldane (1935) that haemophilia would be rapidly extinguished by natural selection if the gene did not constantly arise anew by mutation. In Pedigree G haemophilia arose either by mutation or else I. 2 was heterozygous. As she had three normal sons and her daughters, II.6 and II.7 had four and three normal sons respectively, the probability calculated by Haldane is $9 \times 17 \times 2^{-12}$, or 0.037. The evidence in favour of mutation is strong but not conclusive. In certain of the other

pedigrees the evidence in favour of mutation was very strong, having a probability of 0.00025.

The genes for colour-blindness and haemophilia may be represented by the letters C and H. Their normal allelomorphs by +. Thus a man is either + + (normal), C + (colour-blind), + H (haemophilic), or CH (colour-blind and haemophilic). A woman is diploid for these genes, because a woman has two X chromosomes whereas a man has but one. She is represented as $\frac{++}{++}$, $\frac{++}{C+}$, $\frac{++}{+H}$, $\frac{++}{CH}$, or $\frac{+H}{C+}$

The latter two will differ in their progeny. The sons of $\frac{++}{CH}$ women will be mainly normal or colour-blind haemophilics. Those of $\frac{+H}{C+}$ women will be mainly haemophilic or colour-blind, but rarely both or neither. The other possible female genotypes are extremely rare viz. $\frac{C+}{C+}$, $\frac{C+}{CH}$, $\frac{+H}{+H}$, $\frac{+H}{CH}$, and $\frac{CH}{CH}$

It is possible that the $\frac{H}{H}$ genotype is inviable as it implies that the woman should be a haemophilic.

Pedigree G contains the only example of crossing-over in the material examined. It is possible that II.4 is a mosaic who was originally $\frac{++}{C\ +}$ but in whom a portion was mutated to $\frac{+\ +}{C\ H}$ or $\frac{+\ H}{C\ +}$, in which case both types of tissue would be present in her ovaries and although the probability is not great it is possible. Crossing-over will not be conclusively demonstrated until it occurs in the gametes of a woman who could not be a mosaic.

Bell and Haldane concluded that the linkage investigated between colour-blindness and haemophilia was so close that on quite a small amount of material it was demonstrated without leaving grounds for reasonable doubts. Since haemophilia can be detected before colour-blindness, this study has got no prognostic significance, but if an equally close linkage could be found between the genes determining blood groups and that determining Huntington's chorea, we should be able to predict in many cases which children of an affected person would develop the disease.

The probability that the results attributed to linkage could have arisen by sampling is less than 4×10^{-6}. Bell and Haldane assumed that the frequency of crossing over was as likely to lie below 5 % as above it.

Shortly after the publication of this work by Bell and Haldane Pedigree H was investigated by myself (Riddell 1938) and an addendum to it was written by Prof. Haldane. This addendum is included in this thesis as an appendix (Appendix 2). I have been on the look out for further families of this type so far unsuccessfully, but I have had personal communications from Prof. O. Verschuer (Frankfurt) and Dr. P.J.Waardenburg (Holland) regarding pedigrees in which both colour-blindness and haemophilia had occurred. It would appear that clinical work done upon families such as these may contribute material of considerable value to progress in our knowledge of human heredity.

Pedigree G .

A Haemophilic and Colour-Blind Pedigree.

This pedigree was found as a result of deliberate search amongst known haemophilic families in the West of Scotland. It was the first one in which I found colour blindness in association with haemophilia. The details of the pedigree are as follows:

II.4. Mrs. H., aged 52 years (1936), is a healthy working-class woman of small stature. She is the fourth child of a family of seven, three males and four females. Three brothers and two sisters are married and have families. None of them is a bleeder. Her father died when seventy and her mother when eighty-one. She has no knowledge of bleeders amongst her relatives. Her colour vision is normal.

III.1. T. H. aged 33 years (1936), is an unemployed hammerman. He is a healthy looking man and has had no serious illness. He is not a bleeder. In August 1936, he was examined with Ishihara's cards with the following result:- 12:5 6:2 21:- -:- -:5 2:- -:- -:. This indicates red-green blindness. Unfortunately

this man would not agree to more detailed examination. Several attempts were made to get his co-operation without success. When examined in August he informed me that he had no difficulty in reading coloured numbers, which he had seen before when examined for service purposes. This point was inquired into through official channels and the following information was obtained. He was examined in July, 1930, with Ishihara's test with the following result: 12:3 5:2 21:- -:- -:5 2: - -:- -:. With the lamp, green after signal green was called white. Yellow after red was called white. Both with a number three aperture. His central vision and fundi were normal. This man is not a bleeder, but is a colour defective person. He is married and has one daughter aged 7 years - IV.1.

III.2. This woman is a married daughter, aged 29 years (1936). She lives in Canada and has one daughter - IV.2.

III.3. This boy was a bleeder and died when four years old.

III.4. This boy was a bleeder and died when three months old.

III.5. J. H. was also a bleeder and was brought up with great difficulty owing to frequent disabling haemorrhages. He died aged 21 years. Photographs of this member of the family showed a well-developed healthy looking youth.

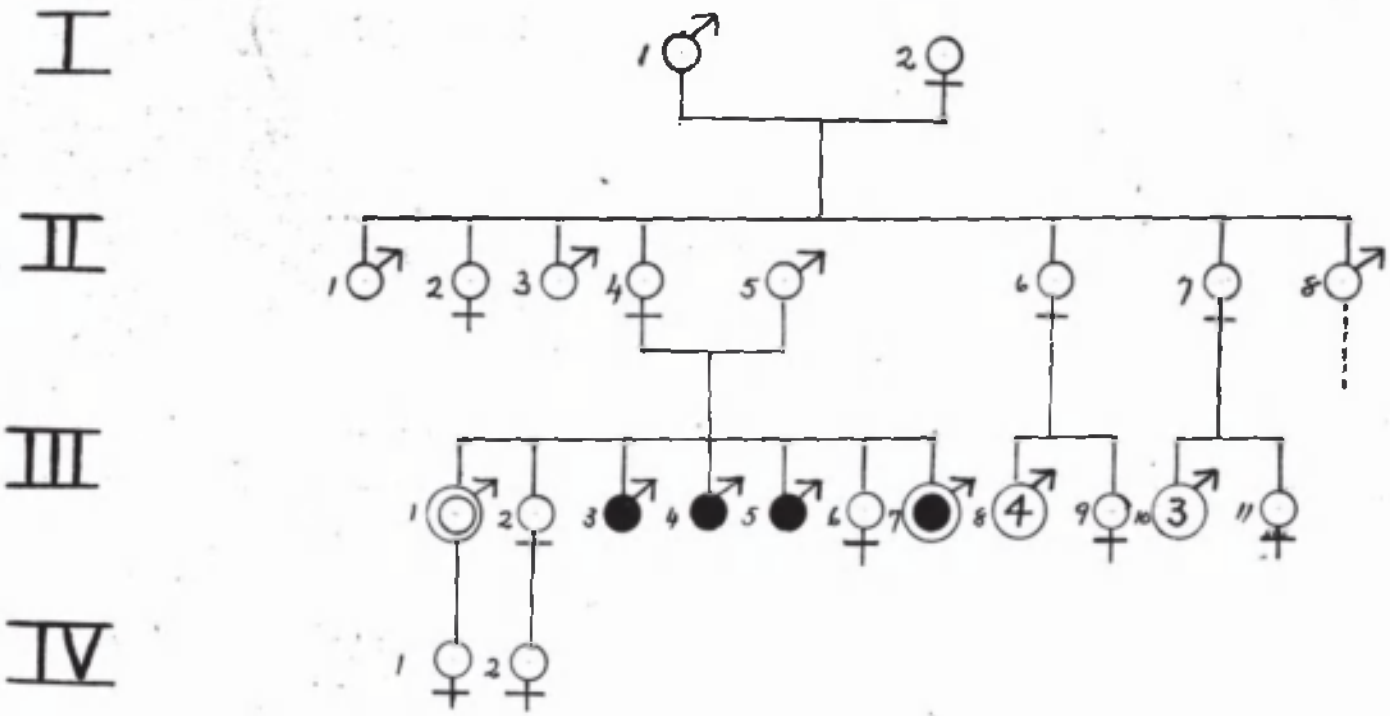
III.6. H. M. is a healthy girl of 18 years. She has never shown any tendency to bruising or of bleedings into joints.

III.7. R. H. is 12 years old (1936). He has bruised easily and has had swellings of his joints ever since he was born. On one occasion he lost blood for a fortnight following upon a tooth extraction. He has been in hospital on two occasions and has required blood transfusion.. Two years ago he was struck on the left wrist by a cricket ball. This injury was followed by haemorrhage into the joints and anaesthesia of the fingers. He subsequently burned his fingers. The tips of three of them became gangrenous and were lost. He is a well-nourished and healthy looking boy and is normally developed for his age. His education has been handicapped severely owing to his frequent absence from school. In August 1936 he was examined with Ishihara's cards with the following result:- 12:- -:2 21:- -:- -:5 2:- -:- -:. This test

was repeated in October, 1936, when the answers given were the same. The defect was confirmed by means of Stilling's plates (nineteenth edition, 1936, Leipzig). In this series he read Nos.1, 2,7,9,24 and 31 correctly. In plates 16,18,20, 32 and 33 he read one figure correctly and the other incorrectly (these plates consist of two numerals). He was unable to see any figures on Plates 3,4,5,6,8,10,11,12,13,14,15,17,19,21, 22,23 and 34. Plates 25 to 30 inclusive were not used in the test. The test was repeated twice in good daylight. His central vision and fundi were normal. This boy is a bleeder and is colour defective.

HAEMOPHILIA AND COLOUR-BLINDNESS

CHART G



● HAEMOPHILIA

◎ COLOUR-BLINDNESS

◉ HAEMOPHILIA AND COLOUR-BLINDNESS

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PROC. ROY. SOC. SER. "B" AND
BRIT. JL. OPHTH.

Pedigree H.

A Haemophilic and Colour-Blind Pedigree.

The present pedigree resulted from the marriage of a haemophilic to a member of a colour-defective family. They had four daughters. One daughter had a haemophilic son and another a colour-defective son. I am indebted to Dr. Andrew Law of Brodick for getting me into touch with the family. He attended a haemophilic member, IV.16, during his last illness. The only living haemophilic was V.10 and his colour vision was normal. It was reported that V.13 was colour-defective and as this individual lived in England it was only after some difficulty that he was examined. He was found to have defective colour vision.

This fact made the pedigree of great interest and it was investigated more fully. To the right side of the chart the original haemophilic pedigree is shown and to the left the members of the colour-defective family. The link between was provided by III.7 who was married twice. Her first husband was III.8, a haemophilic who died when 29 following

an accident with plate glass. They had four daughters, IV.11, 12, 13, and 14. They have all got normal colour vision. The eldest daughter, IV.11 had three sons all with normal colour vision, but V.10 is a haemophilic. The two middle daughters were unmarried. The youngest, IV.14, had two daughters and one son. Her husband had normal colour vision. The son, V.13, has defective colour vision. The son of V.12 is not a haemophilic but is too young to have his vision tested satisfactorily.

I.1 and 2 were first cousins and lived in the neighbourhood of Newcastle-upon-Tyne. They had three children. The youngest, II.5, had three haemophilic sons and one daughter. This daughter was known to have married and had a family, but no more details were available. The only surviving member of the family of II.3 was III.14. His colour vision was normal.

In the colour-blind side of the pedigree one surviving colour-defective person was found, IV.10. He is a step-brother of the four sisters and is a draughtsman by trade. He has occasional difficulty with red lines in a drawing. Examination revealed a gross colour defect. It is well known that draughtsmen and engravers are frequently colour-blind (Bell, 1926). I was informed independently by IV.10

and 14 that IV.4 was very anxious to go to sea as a young man, but was unable to do so owing to defective colour vision. He lives in Canada and has lost touch with his relatives in this country. IV.12 and 13 informed me that their grandmother used to say that it did not matter what colour of dress they wore as far as her husband was concerned. This matter seems to have been a family joke. My enquiries regarding colour vision in this branch of the pedigree caused no surprise, because they all seemed to know something about it being in the family. Therefore II.1 and IV.4 are indicated on the chart as colour defectives.

The various members of the pedigree who have been examined are marked with a star. One haemophilic with normal colour vision, two colour-defective individuals, and ten normal people (including the husband of IV.14) were found. Particulars of the individuals in the pedigree are given as follows:

I.1 & 2. were first cousins and lived near Newcastle-upon-Tyne.

II.1 Was well over 70 when he died and was known to have defective colour vision by IV.13 and 14.

II.4 Nathaniel S. not a bleeder.

II.5 Mrs. D.

III.1 James H. lived in London and was a lithographer. Nothing is known of his vision, but his occupation is of interest.

III.2 Victor Emmanuel H. was not married. A joiner by trade.

III.3 Magnus Samuel H. was married and had two daughters.

III.4 Barbara H. was not married.

III.5 Jean H. (Mrs S.) had three children.

III.7 Elizabeth H. was married twice. Her first husband was III.8 and her second III.6. She had eight children, four in each sibship.

III.8 John L. was definitely a bleeder. He was a jeweller and died as a result of putting his elbow through a show-case. He lived in the south of Scotland.

III.9 Mrs. B. was the mother of a haemophilic, IV.16.

III.10 Mrs. D. had six children, none of whom was affected.

III.11 Mrs. M. had no family, III.12 and 13 were not married.

III.14 James L., aet.70 (1936), was the youngest of the family. He is a plasterer by trade. Never had any haemorrhages and his colour vision was normal. Examined.

III.15,16 and 17. John D., Nathaniel D., Cuthbert D. were all bleeders and died when young. Their sister Bella, III.18, was married and apparently had a family, but even her married name was not recalled.

IV.4 Alfred S. lives in Vancouver. Desired to go to sea as a young man, but was unable to do so owing to defective colour vision. This statement was made by IV.10 and IV.14 independently. They have lost touch with Him.

IV.5 & 6 are both dead.

IV.7. Mrs. L. is dead. She had two daughters.

IV.8 John B. lives in Toronto. As far as is known his colour vision is normal.

IV.9 Annie B. was unmarried.

IV.10 Frank B., aet. 50, is a draughtsman. He had no complaint about his vision except that he had difficulty with red lines when doing a tracing. He is a non-smoker. He was examined with Ishihara's Plates, 4th and 7th editions, Stilling's Plates, 19th edition, and with the bead test (Meyrowitz). He failed in all of them. When tested with Ishihara, 4th edition, his readings were 12:- -: 2 21:- -:- -:5 2:- -:. With the bead test he was unable to find a suitable hole for five obvious yellows, four greens and three reds.

His red, yellow and blue selections were correct as far as he went. His green collection consisted of one green bead, seven purple, one scarlet and one blue. Examined October 1937.

IV.11 Mrs McR. Ishihara's test was normal. Examined July 1936.

IV.12 &13. Miss Isa L. and Miss Elizabeth L. were both examined with Ishihara's test and found to be normal. Examined December 1937.

IV.14 & 15. Mrs. and Mr. S. No colour defect found October 1937.

IV.16. Archibald B. Died in 1931, aet. 40. Was known to be a bleeder. Had bleedings into joints. He was an amateur conjuror and nearly died as a result of juggling with glass bottles when he cut his arm.

IV.17 Andrew D. was not a bleeder. Died aet. 11 from disease of the spine.

IV.18 John D., aet. 37 (1936). Colour vision normal and not haemophilic. Examined July 1936.

IV.19 Robert D. Died aet. 37 (1926) as a result of a motor accident in Canada. Not a haemophilic.

IV.20 Elizabeth D. (Mrs R.), aet. 45, is married and has one daughter.

IV.21 Mary D. (Mrs D.) is married, but has no family.

IV.22 William D., aet. 42, is a marine engineer. He is not a haemophilic and is not colour-blind. Examined December 1937.

V.8 Donald McR., aet. 36, is not a bleeder and has no colour defect. Examined July 1936.

V.9 John McR., aet.34, is not a bleeder and has no colour defect. Examined July 1936.

V.10 Duncan McR., aet. 31, is a definite haemophilic but is not a colour defective. He gets haemorrhages into joints and has had several blood transfusions both preceding and following teeth extractions. Examined July 1936.

V.11 Mrs. W. aet. 33. Has no family.

V.12 Mrs. A., aet. 27, has one son 18 months old.

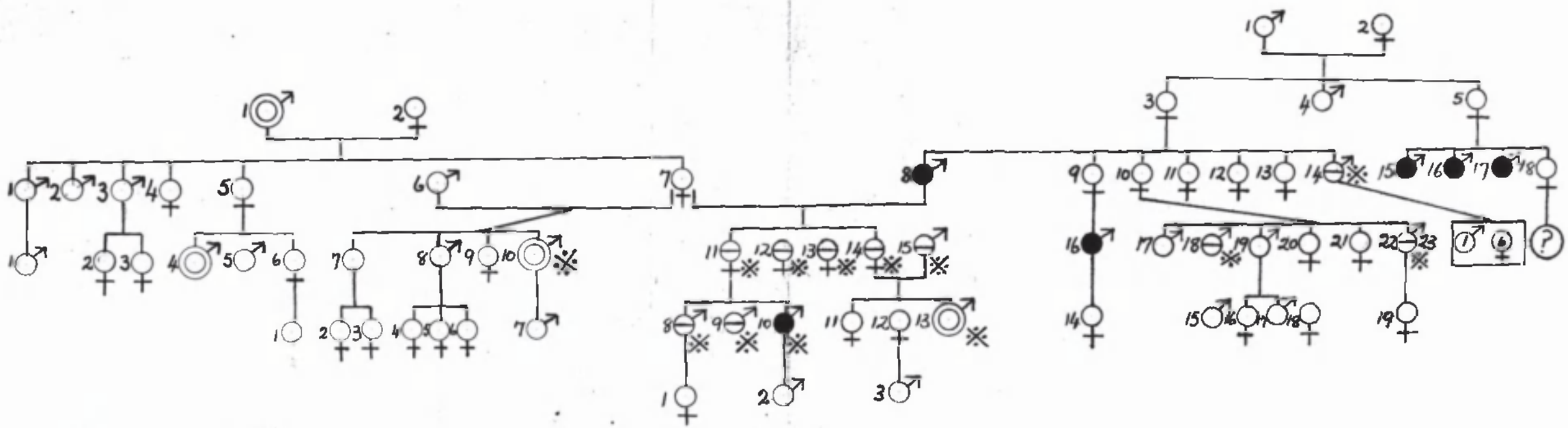
V.13 Tom S., aet. 25, is not a haemophilic. His colour vision is defective. He was examined with Ishihara's Plates, 4th and 7th editions, Stilling's Plates, 19th edition, bead test and the Edridge-Green Lantern. He failed in all tests. With the Ishihara test, 4th edition, the readings were 12:3 5:2 21:- -:- -:5 2:- -:. On the Edridge-Green Lantern with aperture No.6 he called signal green "blue" and red B. "dull yellow". With aperture No.4 he called red B. "red", signal green "white", purple "blue", clear "white", green "red", yellow "red". With aperture No.2 red B. "red", signal green "blue", yellow "red", green "yellow" and red A. "red". Examined September 1937.

V.14 Margaret B. is an only child. She is not married.

VI.3 Is 18 months old. He is not a haemophilic as far as is known, but his colour vision has not yet been investigated.

HAEMOPHILIA AND COLOUR-BLINDNESS

CHART H



● Haemophilic
◎ Deuteranope
⊖ Normal colour vision.
※ Examined

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JOURNAL OF GENETICS

"Some medical geneticists are so greatly impressed with the importance of the statistical method that they actually regard genealogical research as unscientific. This is a most unfortunate attitude, for genealogical research has been and will always remain the foundation of the study of human heredity."

Prof.Fritz Lenz.

Part III.

Blue Sclerotics and Associated Conditions.

This part of the thesis is concerned with Blue Sclerotics, Brittle Bones and Deafness. Pedigrees I and J were worked out some years ago and were included in the "Nettleship Memorial Volume" of the Treasury of Human Inheritance. Pedigree K was found to contain colour defective individuals and the blood group and phenyl-thio-carbamide reactions were also investigated. This pedigree is to be published in a forthcoming number of the Annals of Eugenics.

Pedigrees I and K were found in the West of Scotland. It is of interest to record that Stevenson and Cuthbertson (1931) reported four pedigrees also from the West of Scotland, and that Dr. Usher in a personal communication informed me that he had only seen one such case in his wide experience of hereditary eye disease. His pedigree contained one affected individual. Two other single cases have been reported in the British literature (Hunter 1927 and Stevenson and Cuthbertson 1931). It is curious that six should be reported from one part of Scotland and only one, and that a small one, from another. An analogous position is to be found in the literature of brachydactyly. Most brachydactyls are confined to a small locality in North Wales (Hogben 1939).

There is little doubt that more than one inherited factor is concerned in the production of this syndrome. One clinical feature in common is the blue sclerotics, the other features may occur separately, but blue sclerotics are only found in association with one or more of the group. This fact makes the single case pedigrees of the greatest interest. If we assume that such a case arises from mutation or from linkage of two factors, one contributed by each parent, the establishment of such a syndrome becomes possible. If such a person married a carrier of otosclerosis this part of the syndrome might become accentuated. There is some evidence of this in Pedigree K where the family of IV.12 and 13 are deaf at an earlier age than in the other families in the pedigree and the incidence of myopia is marked. The blue sclerotics were transmitted by IV.12, but IV.13 has a family history of myopia and if we assume that she was a carrier of otosclerosis as well, the accentuation of these features might be accounted for.

I am aware that these suggestions are speculative and that there are other obvious possibilities, for example myopia, or rather the factors concerned in myopia, might have a modifying influence upon the

genes concerned. This suggestion was made to me by Dr. Gordon, assistant to Prof. Hogben in Aberdeen. Such modifying gene effects are well recognised in animal genetics.

In the first family, Pedigree I, no other conditions were observed except those associated with the classical syndrome. The second family, Pedigree J, proved to be of very great interest, because on looking into the history it was found to fit in with accounts previously published by Bishop Harman (1910) and Sydney Stephenson (1910 and 1915). It is of great importance that histories such as this should become linked together as fresh information becomes available. Many problems arise in human heredity which cannot be studied without extensive pedigree material. That this may extend over long periods is well shown by the Nougaret night blind pedigree already referred to, which has been traced for three hundred years. Knowledge of the haemophilics in the Royal Houses of Europe is another example of a pathological pedigree, extending over several generations, and fully studied.

The third blue sclerotic pedigree, chart K, was worked out in considerable detail for other factors.

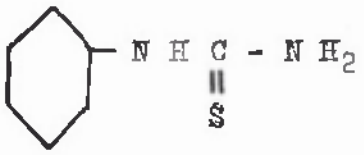
Colour-blind individuals were found and blood grouping and taste-testing were carried out in addition. Thus the family was investigated for at least five hereditary factors with the object of finding out whether or not these factors were being inherited independently. They were the blue sclerotic group, colour-blindness, A - B - O blood group system, the M - N blood group system, and the genes concerned with the ability to taste phenyl-thio-carbamide. As colour-blindness is known to be completely sex-linked and transmitted on the X-chromosome, it would be expected to segregate quite separately from the blue sclerotic group and this was found in fact. The relations of the two blood group systems and the taste factors to the blue sclerotics was quite unknown, because no pedigree had been worked out before. Conditions which are not controlled by factors in the sex-chromosomes are called autosomal. There are in man twenty-four pairs of chromosomes, and it follows that these four conditions are controlled by genes present in one or more of the twenty-three autosomal chromosome pairs. If two or more of them were controlled by genes situated upon the same chromosome pair some evidence of linkage might have been found. This would be analogous to the linkage already described in part II, relating to haemophilia and colour-blindness.

The existence of four blood groups showing differences in their ability to clump together red blood corpuscles was discovered by Landsteiner in 1900. An enormous amount of work has been done on this subject and the hereditary nature of the two agglutinogens, A and B, is completely established. By their presence together or separately or by their absence blood can be grouped as A B, A,B, or O. About ten years ago two more factors M and N were found. These are inherited quite independently of the others and form three groups M, N, and M N. Further factors F, G, H, P, and Q are also known. The practical importance of the original four groups in relation to blood transfusion has tended to relegate the other groups to a subsidiary position in the eyes of clinicians. This view is not the correct one. The more recent blood groups exist in their own right and with independent distributions. "We may look upon the antigenic structure of any individual as a mosaic. It is a very striking and interesting fact that an antigen appears in one species as a species character, whilst it appears in another species as a group character. Thus Forssman-antigen (F) is common to all sheep, whilst in man it forms a part of group character A.

B-like substance is found in all rabbits but in man it is confined to group B. What gives the Landsteiner system its particular stamp is the regular presence of antibodies, the iso-agglutinins, in the serum, but in all probability the occurrence of these antibodies is to be regarded as a secondary feature. Most of the blood grouping systems which we know in man and in animals are not associated with the occurrence of antibodies" (Friedenreich 1938). There are racial differences in the distribution of all the groups established so far. With regard to the inheritance of blood groups, the present view is that there are for the A - B - O system three blood-grouping genes all localised in the same chromosome. In their particular location in the chromosome and in each chromosome partner, is either the A gene, the B gene, or the O gene, with A and B dominant to O. Thus a mating of A and B may result in all four phenotypes appearing if both A and B are heterozygotes. (Friedenreich 1938).

The manner in which the taste test was developed is of interest. This peculiar property of phenyl-thiocarbamide, upon which the test depends, was discovered

by Fox (1932) in America. It is a white crystalline powder and is 0.26% soluble in water at 18°C. and 5.93% at 100°C. Its chemical formula is:-



Dr. Fox had prepared some of this substance and was putting it into a bottle, when a colleague Dr. Noller, complained of the extremely bitter taste of the powder. Dr. Fox was unable to taste it himself. The matter was investigated by Blakeslee (1932) who found that 40% of people were non-tasters. Furthermore it was found that if two non-tasters married, their children were also non-tasters. Tasting parents may have non-tasting children, because the ability to taste (T) is dominant to non-tasting (t), so that parents may have the constitution Tt, in which case non-tasting children may arise. If they are homozygous, TT, then all the children will be tasters. A considerable literature has arisen on this subject and the test has been used in the study of twins, Friedreich's ataxia and major brachydactyly. The

unfortunate term taste-blindness has been used in relation to this test. The association of the word "blindness" with its serious implications to a chemical response which is of scientific interest and only applies to one group of substances seems to be unnecessary.

Various methods have been described for carrying out the test and the method which I employed was recommended by Prof. R.A.Fisher to Boyd (1937), with the addition of a bottle of plain tap water. The patient to be tested is given a tea-spoonful of this to taste followed by a tea-spoonful of P.3 solution (0.00063 %) and then a tea-spoonful of P.6 solution (0.005 %). He is recorded as tasting or not tasting the various solutions. A strength of one part in twenty thousand divides the world into two groups, tasters and non-tasters. Eastern peoples have in general a higher percentage of tasters, which reaches its highest point in the Chinese. Males tend to show fewer tasters and more borderline cases than do females (Boyd 1937). Gene frequencies can be calculated for the ability to taste phenyl-thio-carbamide, as is done for blood groups.

The development of these 'non-pathological' investigations in human pedigrees is leading to the construction of a battery of tests. Further examples are the inheritance of iris colour and the presence or absence of the ear lobes. A series of patients were examined and the refraction, iris colour and condition of the ear lobes were recorded. This matter is desribed in Part IV. Ophthalmology is in a unique position in relation to these normal factors because in no other specialty is it possible to observe and record accurately such a large number. When these serological, chemical and ophthalmic conditions which are controlled by hereditary factors have been worked out, it will be possible to approach the pathological pedigrees from a fresh angle. These normal factors will provide as it were a genetic framework into which pathological factors will be fitted. It is of great importance to establish the homogeneity or heterogeneity of various populations for all these factors. Obviously this entails a vast amount of tedious work in a field which is at present unexplored. It might be possible in the distant future to identify heterozygotes. In practice this would mean that recessive carriers of conditions such as retinitis pigmentosa would be identified and unsuitable matings discouraged.

The findings in Pedigree K are negative as far as linkage between the various factors is concerned. The establishment of such a negative has a certain value. Obviously the chances against any two autosomal factors being carried upon the same chromosome is twenty two to one. By increasing the number of factors investigated the chances are reduced and it becomes more likely that some inter-relation may be found. Further advances in knowledge may increase the importance of such records. A good example of this is to be found in a pedigree of retinitis pigmentosa placed on record by Simeon Snell in 1903. Thirty-three years later Haldane pointed out the presence of partial or incomplete sex linkage in certain human pedigrees and on searching the literature this excellent example was found.

The work done upon Pedigree K has already been referred to in a paper by myself (Riddell 1939b) and it is to be published in detail in a forth-coming issue of the "Annals of Eugenics". It is the largest pedigree of the condition which has been reported and the first to be worked out for linkage investigation.

Pedigree A.

Blue Sclerotics.

In this pedigree blue sclerotics occur in six males and eight females of four generations. A significant feature of the history is the freedom from associated defects or the slight degree of severity in the symptoms associated with blue sclerotics when they do occur ; thus of the fourteen affected members only three were known to have suffered from fractures and in no case does the history justify the diagnosis of fragilitas ossium ; again in each of the four cases of associated deafness the defect was slight. There is no record of consanguinity in the pedigree.

I.1 and 2.No information available.

II.1 died aet. 86 ; he was married but had no children ; he was believed to be normal.

II.3,believed to be normal, died aet.95; he had six sons of whom one,III.3,was reported to have had grey-blue sclerotics.

II.5 is reported to have had blue sclerotics and to have been slightly deaf; her only daughter,all her five grand-children and four of her eight great-grandchildren were affected.

II.6 died aet.60 of bronchitis; a photograph of him showed a square prominent forehead and he was reported

to have had slightly blue sclerotics; he was not known to have had any fractures.

Of the children of II.3 :-

III.2,the eldest,believed to be normal,had four normal children aged 22,20,13 and 5 years respectively.

III.3 died aet. 48 of pneumonia and was unmarried.

III.4 and 6 were normal and married but had no children.

III.5 could not be traced.

III.7 died in infancy.

None of this sibship was seen by me.

III.9,who died aet.47 was reported to have had blue sclerotics and to have been "slightly dull of hearing"; she had five children of whom IV.5 was seen at the age of 48, she had blue sclerotics and brown irides with a marked arcus senelis; the refraction was hypermetropic with some astigmatism; tension was normal; hearing was normal and her teeth were fairly good ; she had fractured her right elbow when about 6 years of age as a result of a fall when standing on an empty box; at the age of 16 and again a few years later she had sprained her left ankle and been laid up for a week; her skull showed a slight occipital protuberance.

IV.6 was seen aged 45, she had blue sclerotics and brown irides with marked arcus senelis; the eyes were prominent and the patient was slightly deaf ; teeth were quite good; there was a history of a fracture of the right patella at the age of 6 when she was knocked over by a dog and

some injury to her right knee in I925 which was followed by marked stiffness; no other joints were stiff; her skull showed very marked occipital protuberance,marked parietal protuberance and less marked frontal prominence.

IV.7,aet.4I,had dark blue sclerotics and brown irides with marked arcus senelis; he had slight exophthalmos and the refraction was slightly hypermetropic,vision 6/6; hearing was normal; there was a history of three fractures, two of which followed perhaps adequate cause,thus,at the age of I6 he fractured his right elbow from knocking it against a railway carriage ; at 34 he fell six feet off some staging and fractured his os calcis; at 4I he fell into a man-hole and fractured his left humerus; the fractures healed and the functional result was good; his skull showed frontal and occipital protuberances; this patient had a positive Wassermann and a double aortic murmur with "waterhammer" pulse; the thyroid was not prominent.

IV.9 was seen aet.40; he had grey sclerotics and greyish green irides, arcus senelis was not present;hearing was good; teeth were bad; his general development was fairly good and there was no history of fractures or of dislocations; he had been under treatment in I922 for six months for some skin lesion; the patient has since died of carcinoma recti.

IV.IO, seen aet.38, had grey sclerotics,irides were green with brownish spots; there was no arcus senelis; visual acuity was 6/6 and a low degree of hypermetropic astigmatism was present; fundi healthy and showed no evidence of arteriosclerosis; there was no exophthalmos and the tension was normal; this patient was slightly deaf, he had very good teeth and no history of fractures or of dislocations; skull was normal, and his general development excellent; height was 5 feet II inches.

Thus all members of the sibship IV. 5,6,7,9 and IO were affected and the two members who were married had affected offspring.

IV.7 had five children of whom one son and two daughters are said to be affected; detailed information about these children was not available.

IV.IO had three children of whom one, V.7,was affected.

V.7.,aet.I2, had blue-grey sclerotics and brown irides; she had no arcus senélis; visual acuity 6/6 with a low degree of hypermetropia; she had no exophthalmos; fundi were normal but darker than those of her twin sister and there was a small quantity of pigment around the borders of the discs; she was not deaf and had good teeth;there was no history of fractures or of dislocations; this patient was well developed for her age but was three inches shorter than her twin sister whom she did not resemble.

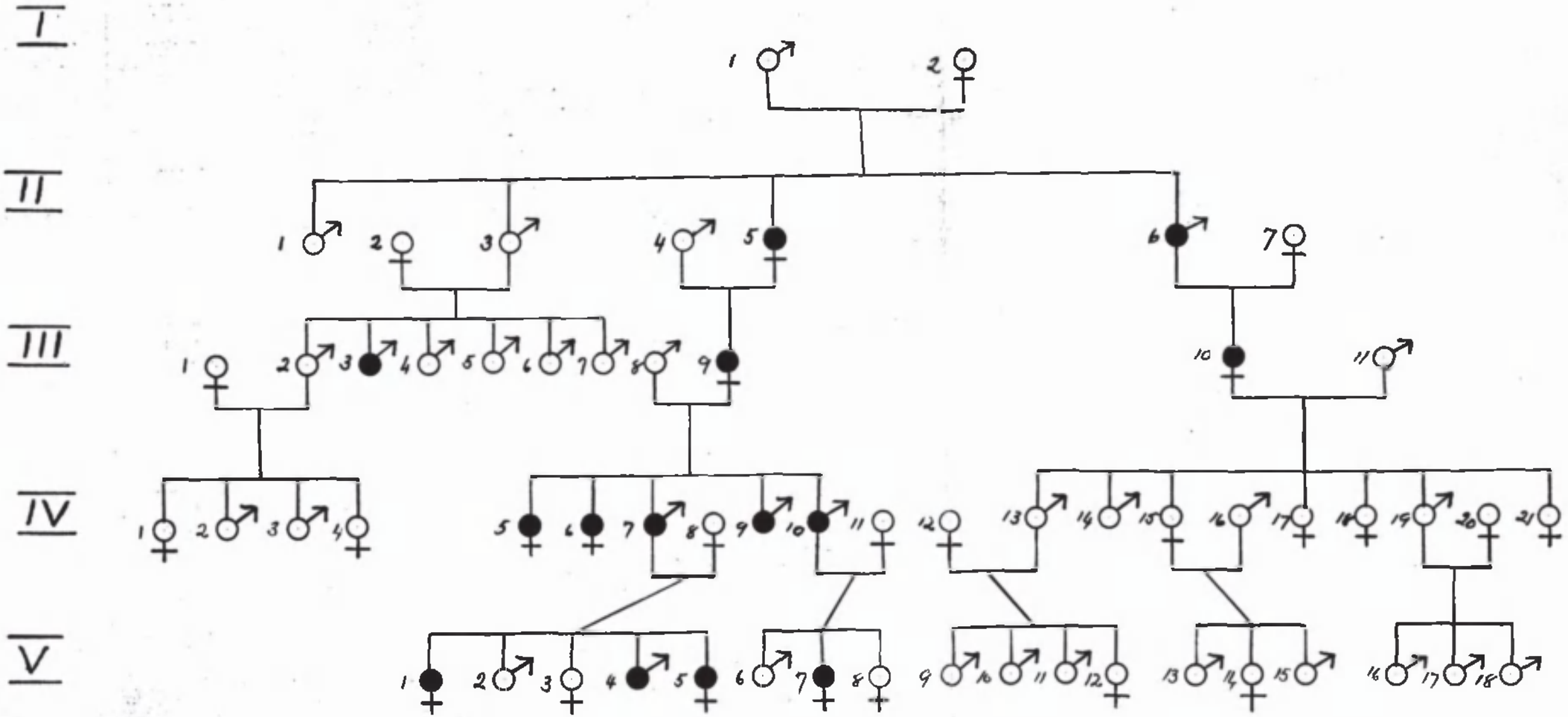
V.8, the twin sister, was very well developed and was normal; the sclerotics were white; the irides blue; the

fundi were healthy and she had a small amount of pigment around the discs; she had a low degree of hypermetropia.

II.6 had one daughter, III.IO, who died aet.55 from pefnicious anaemia; she was said to have been dark with brown irides and blue-grey sclerotics, a photograph showed that she had prominent frontal bossing; she was frequently taken to be a sister of IV.6 as they were "so alike", especially about the eyes; she had had no fractures.
III.IO had seven children of whom four died in infancy, three were normal and had normal children.
IV.I3 was examined aet.44, irides were blue and he had four perfectly healthy children with blue irides and fairish hair; one if these children, V.9, broke his leg at the age of 9 when a door swung back on him whilst at school.
IV.I5 was seen aet. 4I; she had blue-grey irides with normal sclerotics, visual acuity was 6/6; she was not deaf but had bad teeth which were "soft and broke away"; she had a fracture of her left leg at the age 8-IO years.
IV.I5 had three children, the two eldest were healthy and normal; V.I5 had frontal and occipital protuberances and the teeth were bad; he was a big healthy boy ,aged 6, when seen but he had a congenital hernia; he had normal sclerotics and had no fractures. Photographs of V.I3 and I4 showed that they also had prominent foreheads.

BLUE SCLEROTICS

CHART I



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Pedigree J.

Blue Sclerotics.

The pedigree contains forty-one cases of blue sclerotics, some of which are associated with bone fragility and deafness, in five generations. This extremely interesting history was first published by Stephenson in 1910 when he examined a number of the descendants of II.3; later in the same year Bishop Harman, who had come in touch with III.I2, worked out the history of her branch of the family and published a considerably extended pedigree. In 1915 Stephenson described and presented three cases, III.8,IV.I5 and IV.I6, before the Ophthalmological Society and the account there given of the family was not altogether consistent with the former published accounts; a letter to him brought no satisfaction as he had lost touch with the family and was not able to throw any light upon the discrepancies. In 1926 III.I2 again presented herself at Moorfields and I obtained from her a considerable amount of information regarding her family: The pedigree in its present form was completed by Dr.Julia Bell. There are a good many serious differences between the pedigree here presented and that formerly published by Stephenson, particularly respecting the children of III.6, III.8 and III.I0 but,as already stated,there were reasons for doubting the accuracy of the earlier pedigree. Dr.Bell examined III.6,IV.6 and IV.24, who gave detailed accounts

of each member of their families and moreover the account given by them of the children of III.8 agreed entirely with that published by Stephenson himself in 1915. Further, valuable additions which Dr.Julia Bell and myself have been able to add to the pedigree are almost the whole of Generation V and the investigation of the associated defects which were not referred to in the earlier account.

I.1 died aet.60 years; her grandchild,III.12, had seen her and remembered that she had blue sclerotics. The four children of I.1 all had blue sclerotics.

II.2, the only son, died aet. 90; he had three children of whom III.1 was drowned and no knowledge could be obtained about his sclerotics.

III.2, still living and aged over 70 (1927) and had at least two children of whom no information was available; he had blue sclerotics.

III.3 is known to have had blue sclerotics.

II.3 had blue sclerotics; she died aet.80 having had a son and three daughters all of whom had blue sclerotics.

Thus,III.4 had blue sclerotics but was not deaf and had no bone fragility; he was an acrobat on the stage and died as a result of twisting his internal organs whilst "looping" in the air; perhaps his calling in life suggests that he had hyperextensibility of ligaments which is fairly common in association with blue sclerotics.

III.6, aet. 64 (1927), was seen by Stephenson in 1910 and was re-examined by Dr.Bell; her sclerotics were of a deep leaden blue colour and she had complete arcus senelis surrounding each cornea; she was short and slight but very active, not at all deaf and never had had any fractures; she devoted herself to nursing in the intervals of looking after her family; she had been married twice. By her first marriage, III.6 had five children of whom 1 V.1, a son, died aet. 4 months and his mother had no recollection of the colour of his sclerotics.

IV.2 was said by her mother to have blue sclerotics; she had one fracture of her arm when she was small resulting from a slight injury, and she is very deaf; she began to notice her deafness soon after her marriage at the age of 21 years.

IV.4 has normal eyes, is not deaf and has had no fractures; his five children were also free from any abnormality in these respects.

IV.6, seen by Dr.Bell at the age of 40 (1927), had deep blue sclerotics, no arcus senilis or embryotoxon; she became deaf at about the age of 30 but was less deaf than her sister IV.2; she had some injury to her ankle at birth which had always been weak and sprained very readily.

IV.8 died aet $2\frac{1}{2}$ years following measles; he had white sclerotics and had had no fractures up to the time of his death.

By her second husband III.6 had three sons, of whom IV.9 was seen by Stephenson at the age of 6½ years when his sclerae presented a curious uniform bluish tinge perhaps best described as "leaden" ; the appearance extended to the cornea and beyond the equator of the eyeball as far as could be seen ; there was no accentuation in the ciliary zone; he was a lad of dark complexion and a small embryotoxon was present towards the upper margin of each cornea ; fundi were well pigmented and the optic discs of oval shape with a congenital crescent at the lower margin of each papilla ; he had some trouble at that time with his vision,due to compound hypermetropic astigmatism which was not excessive however in grade ; his mother reported that IV.9 fractured his tibia at about the age of 5 years from a slight cause and that he is rather deaf, but his cousin,IV.24,said that his limbs are very brittle and deformed ; it may be that he has had fractures without realising their occurrence ; he was married but had no children.
IV. IO and II had white sclerotics and were unmarried ; they have neither had fractures nor are they deaf.

III.8, sister to III.6, was in bed (1927) encased in plaster with a fractured spine and many fractured ribs as a result of falling downstairs ; the family reported that they "dare not take off the plaster lest she should fall to pieces"; her nephew,IV.24, said that

she had broken every limb and that her bones still,at the age of 61, break very readily ; she was very deaf and had dark blue sclerotics of a leaden hue ; Stephenson saw her in 1915 when she was 4 feet 10 inches in height at the age of 50 ; her sister said that she had an arcus senilis surrounding the cornea. Of the six children of III.8, IV.13 had blue sclerotics and Stephenson reported a fracture of her leg at the age of 3 years ; she was not deaf ; at the age of 27 her height measured 4 feet 10½ inches. IV.15 was described by Stephenson in 1915 ; she had blue sclerotics and is now (1927) deaf, she had had no fractures but had sprained both ankles several times. IV.16 had blue sclerotics and was not deaf ; Stephenson saw her with her mother when she was aged 20, the mother then said that she fell out of bed at the age of 2 years and fractured her thigh ; at 4 years she broke her leg by falling whilst running across the kitchen floor, she sprained her ankle several times and her mother "got quite used to picking her up broken". IV.18 had blue sclerotics but was not deaf and had had no fractures. IV. 19 and 20 had normal sclerotics and were not deaf, but IV. 20 had a history of a broken leg at the age of 3 years.

III.10, the fourth child of II.3 died from "inflammation of the spine"; she had blue sclerotics, once had a fractured jaw and had a history of repeated

sprains ; she was not deaf ; she had six children of whom IV. 2I was still-born and IV. 22 died aged a few days ; nothing was known of the eyes of these two siblings. IV. 23 had blue sclerotics and was not deaf ; she had had no fractures but had suffered from repeated sprains. IV. 24 had deep blue sclerotics and was not deaf ; he was short and of slender build ; he had a broken leg at the age of 3 years, fractured his left arm at I6 and had broken his nose whilst boxing, but he maintained that he had no bone fragility and that all his fractures occurred from severe injury ; he was employed in a motor works and had to wind up heavy cars, which he did without difficulty ; he was a very intelligent man of energetic habits. IV. 26 was killed in the war and was said to have had normal eyes. IV.27 had white sclerotics, no history of deafness and no fractures.

II. 5, the third affected child of I. I,died aged 52 ; her daughter reported that she had blue sclerotics, was deaf, and had on one occasion broken her ankle ; she had a daughter and two sons of whom the sons had normal sclerotics and no history of fracture ; III.I4 died aet. 42, was married but had no children ; III.I5 was alive (I926) aged 50, had two living normal children and two sons who had died aged 2I and I4 days respectively and who are said to have had normal sclerotics.

III. I2, seen by Bishop Harman in I9I0, was then aged 47

and had slaty-blue sclerotics, dark brown hair and brown dark irides; the visual acuity was 6/6 ; the discs were oval and early senile lens opacities were present. She was examined by myself in 1926 when she had well marked arcus senilis and was not deaf; Her right lens was extracted by Mr. Malcolm Hepburn in 1925 ; she fractured her left femur at the age of about four years; slight bossing of the skull was noted but there was no evidence of rickets ; she maintained that "she lost a lot of blood when cut" ; periods ceased at the age of 52 years ; she had had ten children, six of whom were still living.

IV.29 her eldest daughter wrote "I am aware that my eyes are of great interest to nearly every doctor I meet"; she broke her right arm at 9 days and again at 4 years, at a later date her left arm had been fractured and also a collar bone; her mother said that she bruised very easily; she herself said that her hearing was very good; she was aet. 44 in 1926. IV.29 was seen also by Bishop Harman in 1910 who described her very deep slate-blue sclerotics and said that the colouration was more intense over the ciliary regions ; her hair was then a dull gold and the irides a dark green ; she had then one child, a boy, V.17, aet. 2½ years, whose sclerotics were blue but less markedly so than his mother's. IV.29 had in 1926 three children; the boy, V.17, died in 1920 and of the girls V.18 was normal and V.19, aet. 4 years,

had blue sclerotics not quite so pronounced as her mother's. IV. 29 wrote that all her children were born with blue sclerotics but that the first two(V.I7, see above) "lost the blue" in the first twelve months ; the children heard well and had no broken bones.

IV.30 aet. 42 (1926) and his two children had normal sclerotics and had had no fractures.

IV.32 died aet. 2I from rheumatic fever ; he is said to have had blue sclerotics and to have fractured his left arm twice and his left leg twice.

IV.33 aet 39 in I926 had very blue sclerotics and had hadsome injury to his right wrist on one occasion which was possibly a fracture ; he had one daughter aged I2, with blue sclerotics who has twice broken her arm.

IV.35 died aet. 3½ years from croup ; he is said to havehad normal sclerotics and to have suffered no fractures.

IV.36 died aged I year and 9 months through drinking paraffin ; he is said to have had blue sclerotics and to have had no fractures at the time of his death.

IV.37 in I936 aet. 33 had blue sclerotics ; at the age of 5 years she fractured her left leg and at the age of I0. years she twice fractured her left arm ; her two children, aged 8 and 2 years respectively, have each blue sclerotics ; V.23 broke his right arm at the age of 7. V.24 broke her leg at the age of 2 years.

IV.39 was seen by Bishop Harman at the age of 14 years and was considered by him to have sclerotics which were bluer than is normal though the condition was less pronounced than in her affected siblings ; I saw her at the age of 31 when her sclerotics in my opinion were not blue and she had no arcus senelis,no deafness and no history of fractures ; her one child,V.25, aged 9 years had normal sclerotics and no history of fractures.
IV.41 died aet. 1½ years from teething ; he is said to have had normal sclerotics and no fractures.
IV. 42 was aet. 26 in 1926 and had normal sclerotics and no history of fracture.

II.7 had blue sclerotics ; she died whilst her two boys were young, from a fall downstairs which fractured her spine ; the two boys, III.17 and 18 were brought up by III.6 who reported that III.17 had white sclerotics and that III.18 had blue sclerotics and was very deformed; the latter is dead, but III.17 now lives with IV. 24. neither brother was married.
IV.2 had five children of whom V.1 had white sclerotics and no history of fracture. V.2, with blue sclerotics is said to have been born a cripple ; her grandmother said " that her hips went into her stomach ", but from her account it seemed likely that she had congenital dislocation of the hips. V.3 died from measles at the age of 2½ ; he had blue sclerotics but no fracture up to the time of his death. V.4, with blue sclerotics,

was aet. I4 in I926 and had had a fracture of her arm whilst playing at school. V.5 had white sclerotics and no history of fracture. IV.6 had three children of whom V.8, aged I7 in I926 had white sclerotics, was not deaf and had had no fractures; V.9 aged I5 had blue sclerotics and had had one fracture at the age of 3 years from falling up a step. V.I0 had white sclerotics and had had no fracture.

IV.I3 had three children, two girls and a boy, of whom the two girls had blue scerotics and the boy had normal eyes. V.I3 had fractured legs at the age of 4 years. IV.I5 had one child with blue sclerotics aged 2 years, who had had a dislocated shoulder. IV.I6 had one child, a boy, with white sclerotics. IV.24 had one child, a boy aged I0 months who had blue sclerotics.

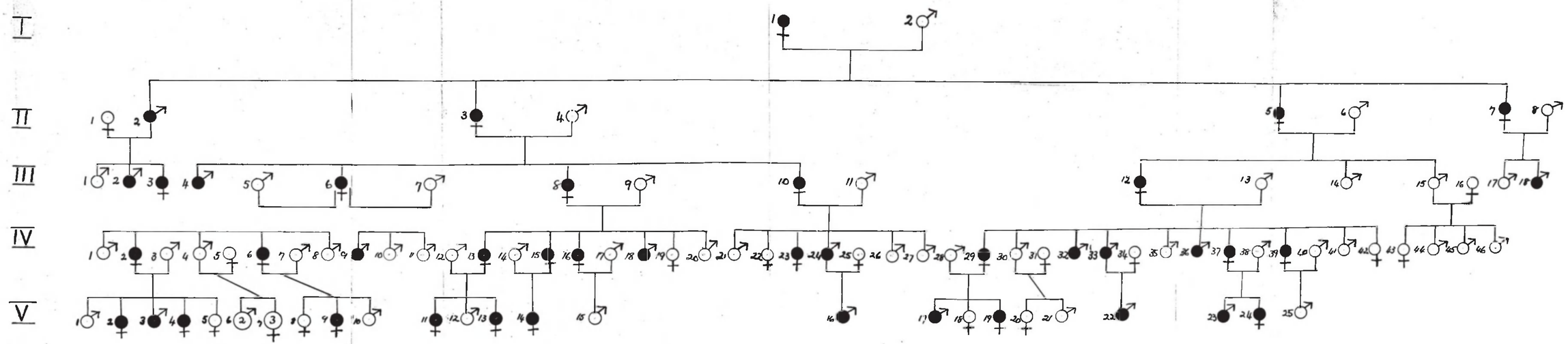
The affected members of this family show varying grades of defect as judged by the depth of colour of the sclerotics and it is an example of the fact that a severe grade of defect as based on this criterion may be, in individuals, unassociated with either of the commonly allied defects. There is little evidence in this family of true bone fragility, though the number of fractures which have occurred in the family are far in excess of what one would expect in a random sample of the population. There is a considerable amount

of deafness occurring amongst the affected members, but again the appearance of this defect does not indicate any criterion as to the severity of the associated defects. All that can be insisted upon is that wherever deafness or a tendency to bone fragility occurs, the sclerotics are blue, but the converse does not hold. No consanguinity was recorded in this pedigree.

BLUE SCLEROTICS

STEPHENSON — HARMAN — RIDDELL — BELL

CHART J



PREVIOUSLY PUBLISHED IN NETTLESHIP MEMORIAL VOLUME

Pedigree K.

Colour Blindness, Blue Sclerotics, Brittle Bones and Deafness.

In the course of a school clinic a boy, VI.30. was brought to see me because he had blue eyes. He came with his sister, VI.33. and they were both found to have well marked blue sclerotics. The boy had had three fractures and the girl one. The father of the children was found to be affected similarly. He informed me that he was a house painter by trade, and as I am of the opinion that a person's occupation is an unreliable guide to the state of his colour vision, I tested him and found his colour perception to be defective. The pedigree was worked out in more detail and it contains two hundred and eight individuals. Of these seventy one live abroad or are dead and twenty two have not been examined. One hundred and fifteen have been seen and of these ninety eight have been tested with Phenyl-Thio-Carbamide and ninety have been blood grouped. Eighty nine individuals have had both tests carried out. The taste-testing and collection of blood samples was done by myself and the blood grouping was carried out at the Galton Research Laboratory for me by Dr. G. L. Taylor and his staff.

Nine males were found to have defective colour vision. Three of them had also blue sclerotics. One boy, otherwise normal, derived his defective colour sense from his mother , who was not herself of the defective stock.

Forty five individuals, twenty males and twenty four females had blue sclerotics or were reliably reported to have been affected. No females with colour defects were found. The tests used were Ishihara's Isochromatic Plates, Fourth Edition (thirteen plates), and Seventh Edition (twenty five plates), Stilling's pseudo-isocromatische Tafeln, 19th. Edition, and in certain cases the defect was confirmed with the Edridge-Green lantern.

The method of using the phenyl-thio-carbamide was that described by William C. Boyd and Lyle G. Boyd (1937) with the addition of a teaspoonful of tap water to begin with. This was followed by a teaspoonful of 'P.3' 0.00063 % Phenyl-thio-carbamide, and then a teaspoonful of 'P.6', 0.005 % Phenyl-thio-carbamide. The patients were recorded as tasters or as non-tasters and the results are shown in Table

The pedigree chart traces the threads of blue sclerotics, brittle bones, deafness, colour blindness, myopia, blood grouping and phenyl-thio-carbamide reactions derived from a hand-loom weaver and his wife ,III.1 and 2.

The hand loom weaver had blue sclerotics, deafness and a history of fractures. He was an only child and died at the age of fifty five. His mother was also a hand-loom weaver, had blue sclerotics and broke her leg. These statements were confirmed by IV.I and IV.I2, but there was great difficulty in establishing the relationship of II.I to the other members of this generation. The history given is that supplied by IV.I who is confident that her statements are correct. The family names which she gave were correct and confirmed by III.7, the husband of III.6. But III.7 denied all knowledge of blue eyes or brittle bones in any of his wife's relations. This difficulty may be solved at a later date when I have traced the antecedents of some affected children in the south of Scotland. Unfortunately, although the County Medical Officer knows that they exist he cannot trace them until they appear in the course of routine school medical examination.

The seven children of the handloom weaver are described alphabetically under headings A to G.

Family A.

The eldest daughter, IV.1. is now seventy-three, and had thirteen children. She has about five dioptres of myopia, and senile lens changes, but is otherwise normal. Neither she nor her husband is very tall, (5ft. 2in. and 5ft. 4in. respectively). Her children are about the same height as their blue sclerotic cousins. The youngest of the family were twin boys, but one was still-born. Three sons are colour-blind, V.1,10,and 23; one daughter, V.8. has a colour-blind boy. There are no blue sclerotic individuals, and none of her children is myopic.

Family B.

The second daughter, IV.3. (1869 - 1894) had blue eyes; her leg was broken by a cricket ball, but she was not deaf. She had five children, some of whom were unaffected, but no details of this family are available because they all went to North America, and have lost touch with their relations in this country.

Family C.

This woman, IV.5. (1871 - 1909) died in Canada, aet.38. She had blue sclerotics, deafness, and broke her arms while skating. She had nine children. Two died

in childhood, and no details are available. Of her seven other children, four had blue sclerotics, and the two examined are both colour blind, as well as suffering from blue sclerotics, deafness, and a history of fractures.

The eldest son, V.30. is a house painter, but has got defective colour vision, blue sclerotics, parietal bossing of his skull, deafness in his right ear, which came on when he was about twenty-five, and a history of two fractured arms, when sixteen years of age. This man has had six children; three had blue sclerotics, and three were unaffected.

Two sons and a daughter live in Canada and I have not succeeded in getting in touch with them so far. One son and the daughter are reported to have blue sclerotics. The youngest son of IV.5. has also got blue eyes, a history of eight fractures, well marked occipital bossing, slight deafness, and occasional tinnitus, which started when he was thirty years of age. His colour vision is grossly defective. He is married but has no family.

The unaffected daughter, V.39. has got four children, two boys and two girls. Three of these children have been examined and are normal.

Family D.

This daughter, IV.7. 1873 - 1937. She had blue sclerotics, deafness, marked tinnitus, and numerous fractures. She had seven children, four boys and three girls. Five of the children had blue sclerotics and the eldest son has got two boys, one affected and one unaffected. Her second son, V.49. has got a colour-defective boy, VI.49.

Family E.

IV.10. (1875 - 1935) was married twice. She had blue sclerotics, was stone deaf, and there was a history of numerous broken bones. Deafness began at the age of thirty. By her first husband she had four children with one affected daughter. This daughter has three girls, two with blue eyes. By her second husband she had three affected children, two boys and a girl.

Family F

This man, IV.12. had seventeen children; four died when very young or were still-born, V.83,84,85, and 86. The correct position of these four births is not known. He is a house painter aged fifty-nine. His colour vision is normal, and he has had only one fracture - a collar bone when eight years of age. He has got blue sclerotics; he is very deaf and suffers from

noises in his head. The deafness started when he was twenty-eight. Of his thirteen surviving children ten had blue sclerotics. He has at present, five grand-children all affected. The deafness among his children has started at an earlier age than in any other family in this pedigree, and is very marked. Two girls of twenty-five and twenty-eight are almost stone deaf. In addition they are myopic and one was born with a tooth.

Family G.

This man, IV.14. is stone deaf and can only be communicated with by signs or writing. He has got markedly blue sclerotics, but only gives a vague history of one doubtful broken bone in his hand when he was a boy. He has three sons, one with blue sclerotics, the other two unaffected. All the members of this family who have been examined are non-tasters of phenyl-thio-carbamide.

As far as I am aware this is the largest pedigree of the condition which has been worked out. In the only other pedigree of blue sclerotics known to me in which colour blindness occurred, those affected were not indentified (Stobie 1924). The detailed histories of the present pedigree do not differ markedly from those previously published. The fractures tend to occur in childhood or in adolescence and heal firmly The early onset of deafness in the family of IV.12 is a striking feature and might be due to a modifying factor introduced by his wife. This suggestion is of course speculative.

The answers given by the colour defective males to Ishihara's Test Fourth Edition are shown in Table 3

The details of the Blood Groups and Phenyl-thio-carbamide tests are set out in Table 4, and are arranged according to the alphabetical family groups A to G.

It is essential in putting this pedigree on record to acknowledge the co-operation of V.16. It would have been an impossible task to trace out all his numerous relations and persuade them to be blood-grouped and taste-tested without his assistance.

Table 7 .

Table showing the different answers which the Colour Defective members of the pedigree gave when tested with Ishihara Isochromatic Plates (Fourth Edition).

Plate No.	I	2	3	4	5	6	7	8	9	IO	II	I2	I3.
Normal	12	8	6	5	74	2	6	5	7	-	-	26	42
V.1.	12	-	-	-	--	-	-	-	-	-	-	--	--
VI.8.	12	-	-	2	21	-	-	-	-	5	2	--	--
V.10.	12	-	-	-	--	-	-	-	-	-	-	--	--
V.23.	12	-	-	2	21	-	-	-	-	5	2	--	--
V.30.	12	3	5	2	21	12	21	-	-	5	2	--	--
V.43.	12	3	-	2	27	-	-	8	9	5	--	--	42
V.55.	12	3	5	2	21	-	-	-	-	5	2	--	--
V.59.	12	-	-	2	21	-	-	6	7	5	2	--	--

Although VI. 49 was discovered to have defective colour vision, he is omitted from the above table because he must have derived his defect from his mother, V.50. His father, V.49, had normal colour perception.

Pedigree numbers and initials of the sixteen members of the pedigree who were neither blood grouped nor taste-tested, although they were examined.

III.7 Mr.M. husband of III.6. He was unable to give any positive information regarding his wife's relatives.

V.2 Mrs. J.T.

V.II Mrs. John T.

V.44 Mrs.Robert John L.

V.45 David C. 1899 -

VI.27 Joyce T. 1934 - .

VI.51 Margaret C. 1929 -

VI.52 James C. 1935 -

VI.53 David C. 1937 -

VI.54 Lily C. 1938 -

VI.57 Ann C. 1936 -

VI.58 Ina C. 1937 -

VI.70 May McC. 1934 -

VI.77 William McC. 1937 -

VI.78 Malcolm W. 1932 -

VI.80 Cathie McC. 1937 -

DETAILS OF MEMBERS OF THE PEDIGREE.

I.1&2. No information available.

II.1. Maria M. a hand-loom weaver; blue sclerotics; deaf; one broken leg; may have been married twice.

II.2. No information.

II.3. First husband of II.4. This sibship childless.

II.4. Mary Ann M. died aet. 60; she had two daughters by her second husband, III.4. and 5. She had blue sclerotics according to IV.1., but her son-in-law, III.7. denied this. III.7. was unable to report any blue eyes, fractures, or deafness in this part of the pedigree.

II.5. Second husband of II.4.

II.6. Married II.7., but although known to have children, the family has not been traced.

II.8. William M. went to sea, and no more is known of him.

III.1. Isaiah McC. died aet. 55; an only child; blue sclerotics; broken bones; deaf; was a hand-loom weaver, and worked with coloured threads in artificial light according to IV.12.

III.2. This woman died aet. 38 from rheumatic fever; she had one sister, III.3. whose son IV.16. was examined for colour. This man's colour vision is normal; he is a hand-loom weaver; examined Dec. 1938.

IV.1,3,5,7,10,12, and 14 were children of III.1. and 2. and will be described as separate families, A to G.

Family A.

IV.1. Born 1866; white sclerotics; no deafness; no fractures; iris blue; patient is myopic, and wears Rt. -5.0. Lt. -4.0. Colour vision normal, but patient's central vision is not good, owing to senile lens changes. Height 5ft. 2in. She has had thirteen children.

IV.2. Mr. T. 1868 - ; colour vision normal; low degree hypermetropic astigmatism; blue iris.

V.1. J.T. 1885 - ; sclerotics white; iris blue; no deafness; no fractures; hypermetropic; colour vision abnormal; Ishihara 4th edition, only 12 could be read; Stilling's Plates, he read 9,58, -,-,5,6,7,-,8,86,-,-,-,56,-,66,-,89,CH,-,2,8,88, 5,92,7, He is married, but has no family.

V.3. Mrs. Annie C. 1889 - ; reported to be normal by IV.1. She is married and has two girls; she lives in Ireland.

V.5. William T. 1891 - ; $V_A 6/6$; sclerotics white; iris grey; colour vision normal; height 5ft. 5½in.

V.6. Mrs. William T. iris blue.

V.8. Mrs. E.G. 1892 - : sclerotics white: iris brown: no fractures: has three children from two sibships: the youngest boy, VI.8. has defective colour vision.

V.10. John T. 1895 - : sclerotics white: iris hazel: no deafness: no fractures: married but has no family: definitely colour defective: Ishihara 4th edition, only the first plate, 12, was read: on the 7th edition he read the first four plates as 12,3,5, 10, and no others. The normal subject reads 12,8, 6,29. This man was examined in failing daylight, but the illumination was good enough for his normal brother, V.15. to appreciate the errors: height 5'9": V.A.6/6 unaided.

V.12. Samuel T. 1897 - : sclerotics white: iris blue: no deafness: no fractures: V.A.6/6: colour vision normal: height 5' 4": married and has four normal children.

V.13. Mrs. Samuel T.: iris grey: V.A.6/6.

V.14. Mrs. Agnes F. sclerotics white: iris brown: no fractures: no deafness: V.A.6/6: colour vision normal: she has had six children of whom three are alive, including VI.14. twin of VI.15. who was still-born.

V.15. Mr. F. hazel iris.

V.16. Alexander T. 1900 - : sclerotics white: iris brown: no fractures: no deafness: V.A.6/6: colour vision normal: married and has four children: height 5' 7".

V.17. Mrs. Alex. T. 1901 - : iris blue.

V.18. Andrew T. 1901 - : sclerotics white: iris brown: no deafness: no fractures: V.A.6/6: colour vision normal: married, has five normal children.

V.19. Mrs. Andrew T. grey iris.

V.20. Charles T. 1905 - : sclerotics white: iris brown: V.A.6/6: colour vision normal: height 5' 3". no fractures: no deafness: married, has one daughter.

V.22. Roland T. 1908 - : sclerotics white: iris blue: V.A.6/6: colour vision normal: height 5' 2".: no fractures: no deafness.

V.23. North T. 1910 - : surviving twin of V.24. who was still-born: height 5' 2": no deafness: no fractures: V.A.6/6: colour vision grossly defective: Ishihara, 4th edition, 12:- -:2 21: - -:- -:5 2:- -: 7th edition, 12:- -:- -:- -: 17 21:- -:- -:- -:- -:5 2:45 73:- -: Stilling's Plates, 9,58,-,-,5,-,7,-,8,-,-,-,-,56,-,43,-,56, -,80,CH,48,88,58,-,98,-. When tested with Edridge Green Lantern, aperture 3, he called yellow "red", blue "green" and green "white". This patient thinks that the sodium lamps, used to light the street in which he lives, are of a green colour.

Children of V.3.

VI.1&2. Not examined; live in Ireland.

Children of V.5.

VI.3. Annie T. not examined.

VI.4. Moira T. iris blue-grey.

Children of V.8.

VI.5. Not examined; married Dec. 1938.

VI.7. James G. 1917 - ; sclerotics white; iris hazel; height 5ft. 9in.; no fractures; no deafness; V_R 6/6, V_L 6/60; operation for convergent squint; colour vision normal.

VI.8. E.M. 1928 - ; sclerotics white; iris brown; colour vision grossly defective; answers similar to his uncle's, V.23., when tested with Ishihara, 4th and 7th editions, and Stilling's Plates.

Children of V.12.

VI.9. Andrew T. 1923 - ; sclerotics white; iris blue; height 5ft. 6in.; no fractures.

VI.10 Margaret T. 1925 - ; sclerotics white; iris blue-grey; V_A 6/6.

VI.11. R. T. 1928 - ; sclerotics white; iris grey; colour vision normal; V.A. 6/6.

VI.12. Ian T. 1932 - : sclerotics white; iris hazel: colour vision normal.

Children of V.14.

VI.13. Marie F. 1922 - ; sclerotics white; iris blue; colour vision normal; WITH MIXED ~~case~~ of astigmatism corrected; V_A6/6, right and left.

VI.14. Sarah F. surviving twin, 1923 - ; sclerotics white; iris hazel; (VI.15. still-born twin).

VI.16. Nan F. 1928 - ; sclerotics white; iris brown.

VI.17. Female, 1934; died aet. 3½ years.

VI.18. Male, 1938; still-born.

Children of V.16.

VI.19. Marion T. 1922 - ; sclerotics white; iris blue; colour vision normal; myopic astigmatism; V_A6/24; J.1. right and left.

VI.20. William T. 1925 - ; sclerotics white; iris brown; V_A6/9; colour vision normal.

VI.21. Alexander T. 1927 - ; sclerotics white; iris blue; V_A6/6; colour vision normal.

VI.22. Helen T. 1931 - ; sclerotics white iris hazel; colour vision normal; V_A6/12.

Children of V.18.

VI.23. Martha T. 1925 - ; sclerotics white; iris grey; history of squint; wearing + 4.0 Sphere, right and left.

VI.24. Elsie T. 1928 - ; sclerotics white; iris blue.

VI.25. William T. 1931 - ; sclerotics white; iris blue; colour vision normal.

VI.26. North T. 1923 - ; sclerotics white; iris blue; colour vision normal.

VI.27. Joyce T. 1934 - ; sclerotics white; iris blue.

Child of V.20.

VI.28. Ella T. 1932 - ; sclerotics white; iris blue.

Family B.

IV.3. Mrs MacC. 1869; died aet. 25; blue sclerotics; broke a leg with a cricket ball; no deafness; had five children, four girls and one boy, some of whom are reported to have blue sclerotics by IV.1. This family emigrated to America and I have not been able to trace any of them.

IV.4. Mr. MacC. no information.

V.25,26,27,28, and 29. No reliable information; in Canada; according to IV.1. some of these children were affected.

Family C.

IV.5. Sarah MacC. (Mrs.L.) 1871; died aet. 38, in Canada; blue sclerotics; deaf; broke both arms while skating; she had nine children; two died in infancy.

V.30. William L. 1895 - : blue sclerotics: iris blue: No arcus:hypermetropic: height 5' 3": has only had two fractures, both in the left arm, in 1911 and in 1912: no dislocations: slight occipital and frontal bossing: deafness came on when twenty-five: no tinnitus: colour vision abnormal: Ishihara, 7th edition, 12:3 5:70 27:2 5:17 21:12 21:21 15:- -:- -: 5 2:43 73:- -:35 96: Stilling's Plates, 9,58, -,2,5,6,7,-,8,-,-,-,-,-,-,-,-,5,6,-,80,-,CH,16,-, 8,58,9,2,45,49. When tested with Edridge Green Lantern, he called green "light blue", and yellow "red". It is of interest that this man's occupation is that of a house painter.

V.31. Mrs. William L. sclerotics white.

V.32. Isaiah L. and his wife, V.33. live in Canada: they have one son, VI.35.

V.34. Mrs. Sarah F. according to IV.1. has blue sclerotics: has had four children of whom one was reported to be blind, by IV.1.

V.35. James L. sclerotics white: not married: died a few years ago.

V.36. Walter L. lives in Vancouver and is in the theatre business: reported to be normal: is married: has one daughter, VI.40.

V.39. Mrs. Nellie W. 1908 - : sclerotics white: iris hazel: no fractures: no dislocations: no deafness: no bossing: has four normal children.

V.41. Robert L. died in infancy.

V.42. Walter L. died in infancy.

V.43. Robert John L. 1908 - : sclerotics blue: iris blue: three fractures in each arm, and two legs broken in childhood: no fractures since 1924: occipital bossing: slight deafness in left ear, came on at thirty years of age: slight tinnitus: height 5' 3": Ishihara, 4th.edition, 12:3 -:2 27:- -:8 9:5 -: - 42: 7th.edition, 12:3 5:70 35:2 5:17 21:- -: 15 -:- -:- -:5 8:45 75:24 4:32 9: Stilling's Plates, 9,58,-,-,5,-,7,-,8,-,-,-,-,-,-,43,56,39,CH,-,-,8, 58,92,48,49. When tested with Edridge Green Lantern, aperture 3, he saw blue "green" and yellow "pink": aperture 2, he saw green "blue" and yellow "red" and blue "more like blue".

Children of V.30.

VI.29. Sarah L. 1923 - : sclerotics white: iris blue: no fractures: no deafness: height 5' 4".

VI.30. Willie L. 1925 - : sclerotics blue: iris blue: fractured right leg, also left arm twice when about six years old: no deafness: slight occipital and frontal bossing: height 4' 8".

VI.31. Still-born.

VI.32. Male, died of convulsions in infancy: father, V.30. states that his eyes were blue: no fractures reported.

VI.33. Jessie L. 1930 - : blue sclerotics: broken right arm.

VI.34. Annie L. 1932 - : sclerotics white: iris blue: no fractures: no deafness: no bossing.

Children of V.39.

VI.42. James W. 1931 - : sclerotics white: no fractures: no deafness: colour vision normal.

VI.43. William W. 1933 - : sclerotics white: iris blue: no fractures: no deafness: no bossing.

VI.44. Catherine W. 1938 - : not examined.

Family D.

IV.7. Jamesina C. 1873 - 1937: sclerotics blue: suffered from deafness: tinnitus: numerous fractures: had seven children.

IV.8. Mr. C. stated that a family descended from a full cousin of IV.7.'s grandmother had blue sclerotics. This family has not been traced as yet.

V.45. David C. 1899 - : sclerotics blue: iris grey: arm broken three or four times: marked parietal bossing: deafness: occasional tinnitus: married: two children, one with blue sclerotics and the other normal: height 5' 3": Ishihara, 4th edition normal.

V.47. Agnes C. 1900 - : blue sclerotics: iris grey: broken arm and leg: double jointed in thumbs and toes: dislocated knee cap: slight deafness: parietal and occipital bossing; one unaffected son, VI.47. who was born with a tooth. His colour vision is normal.

V.49. Sam C. 1903 - : sclerotics white: colour vision normal: has had seven children: six are alive and one boy, VI.49. has defective colour vision: none has blue sclerotics.

V.51. Ina C. 1905 - : sclerotics blue: iris grey: three broken collar bones and broken finger: no double joints: no deafness: height 4' 11":

V.52. Willie C. 1908 - : sclerotics white: iris blue: no fractures: no deafness: height 5' 7½": married: has four normal children.

V.53. Mrs. Willie C. iris hazel.

V.54. Jean C. 1909 - 1923: had blue eyes: no fractures: died of peritonitis.

V.55. James C. 1911 - : sclerotics blue: iris grey: two broken arms: no deafness: no dislocations: slight parietal bossing: colour vision defective: Ishihara, 7th edition, 12:3 5:28 25:2 5:27 21:- -: 18 -:- -:- -:5 2:45 78:20 40:30 94: is married and has one daughter, born February, 1939.

Children of V.45.

VI.45. Neil C. sclerotics white: broken arm.

VI.46. David C. blue sclerotics: broken left leg.

Children of V.52.

VI.55. James C. 1932 - : unaffected: iris grey-blue.

VI.56. David C. 1934 - : unaffected: iris grey-blue.

VI.57. Ann C. 1936 - : unaffected: iris grey-blue.

VI.58. Ina C. 1937 - : unaffected: iris grey-blue.

Family E.

IV.10. Annie McC. 1875 - 1935: sclerotics blue: fractures: stone deaf: married twice: had seven children, four by her first marriage, and three by her second.

V.57. Hughie McC. 1897 - : sclerotics white: iris blue: no fractures: slightly deaf: Ishihara normal:

V.58. Mrs. Hugh McC. hazel-brown iris.

V.59. Willie McC. 1900 - : sclerotics white: iris brown: no fractures: no deafness: height 5' 6": Ishihara, 4th edition, -,12:-,-:2,21:-,-:6,7:5,2: -,-:. Defect confirmed with Ishihara, 7th edition, and Stilling's Plates.

V.61. Mrs. Mary McC. 1902 - : sclerotics blue: broken ankle: no deafness: three children.

V.63. Annie McC. 1905 - : normal: iris grey: no broken bones: slightly deaf: running ear sometimes: not married.

V.64. Thomas McG. 1910 - : sclerotics blue: iris blue-grey: both arms broken several times: dislocations: looseness of joints: parietal and slight occipital bossing: height 5' 3½".

V.65. Fannie McG. 1911 - : sclerotics blue: iris blue: broken ankle: no deafness: not married: height 5'.

V.66. John McG. 1913 - : sclerotics blue: iris grey: height 5' 2½": seven fractures in leg: no deafness: marked occipital bossing and slight frontal bossing.

Children of V.57.

VI.60. Hugh McC. 1918 - : sclerotics white: iris hazel: Ishihara normal.

VI.61. John McC. 1920: died aet. 10 months.

VI.62. John McC. 1921 - : sclerotics white: iris hazel: Ishihara normal;

VI.63. Annie McC. 1924 - : sclerotics white: iris brown: Ishihara normal.

VI.64. Marion McC. 1926: died of meningitis aet. 5½.

VI.65. Elizabeth McC. 1928 - : iris hazel-brown.

VI.66. Willie McC. 1931 - : sclerotics white: iris brown: fractured hip in bus accident: fractured finger.

VI.67. Robert McC. 1933 - : sclerotics white: fractured leg in bus accident.

Children of V.59.

VI.68. Hugh McC. 1926 - : not examined.

VI.69. Ellen McC. 1929 - : sclerotics white: iris grey: no fractures.

VI.70. May McC. 1934 - : sclerotics white: iris brown.

Children of V.61.

VI.71. Nan McC. 1925 - : sclerotics blue: iris brown: right arm broken when two years old: occipital and temporal bossing: no deafness.

VI.72. Rose McC. 1929 - : sclerotics blue: iris hazel: leg broken when aet. 5: slight parietal bossing.

VI.73. May McC. 1931 - : sclerotics white: iris brown: no broken bones: not examined as she was in hospital with diphtheria: information from parents.

Family F.

IV.12. William McC. 1880 - : sclerotics blue: iris dark hazel: broken collar bone when eight years old: slight parietal and occipital bossing: deafness in both ears, right ear worse than left: deafness came on at age of twenty-eight: marked tinnitus: height 5' 5½".

IV.13. Mrs. William McC. 1883 - : iris brown: no deaf relatives: no glasses: has had seventeen children all of whom got their teeth when about

four months: relatives short-sighted: two uncles blind: all adult children 5' 1" to 5' 2".

V.67. Mrs. Christina C. 1901 - : sclerotics blue: two fractures: slight deafness: has two daughters, eldest slightly deaf: both have blue eyes: not examined: information from parents.

V.69. Mary McC. 1904 - : sclerotics blue: iris hazel: fractured arm, leg and collar bone: very deaf: deafness commenced at age of nineteen: no dislocations: no bossing.

V.70. Willie McC. 1906 - 1938: sclerotics blue: no fractures: deaf on return from India: dislocated joint in army when boxing: killed by falling off a scaffold while at work as a house painter: two affected children.

V.73. Mrs. Janet W. 1910 - : sclerotics blue: iris brown: no fractures: no dislocations: very deaf: tinnitus: slight occipital bossing: has one son, VI.78.

V.74. Agnes McC. 1911 - : sclerotics white: iris hazel: no fractures: no deafness: no bossing.

V.75. Maria McC. 1914 - : sclerotics blue: iris hazel: dislocation of elbow and wrist: no deafness: no tinnitus: born with a tooth: occipital bossing: double jointed thumbs and toes.

V.76. Sarah McC. 1918 - : sclerotics blue: fractured leg, arm and collar bone: very deaf: deafness

commenced when thirteen years of age: tinnitus: double jointed thumbs and toes: occipital and slight parietal bossing.

V.77. Robert McC. 1922 - 1924: sclerotics blue: no fractures: died of acute diarrhoea and meningitis.

V.78. Quinton McC. 1920 - : sclerotics blue: iris hazel: fracture of both elbows and broken arms four times, also three or four ribs: slightly deaf: no tinnitus: occipital bossing: height 5' 3".

V.79. James McC. 1921 - 1923: sclerotics blue: fractured leg.

V.80. Annie McC. 1924 - : sclerotics white: iris brown: no fractures: no deafness: no double joints: height 5' 3", taller than the others.

V.81. Margaret McC. 1930 - : sclerotics white: iris brown: fractured collar bone: no deafness: no bossing: double jointed thumbs and looseness of joints.

V.82. Margaret McC. died aet. nine months: sclerotics blue: no fractures.

V.83, 84, 85, and 86 died at birth or in infancy. Exact position in sibship not known.

Children of V.67.

VI.74. Janet C. 1922 - : sclerotics blue: iris hazel: fractured leg, two arms, elbow, and wrist:

deafness following mastoid aet. nineteen years: slight occipital bossing.

VI.75. Agnes C. 1923 - : not examined: blue sclerotics: information from IV.12. and 13.

Children of V.70.

VI.76. Female 1934 - 1938: sclerotics blue: leg fractured three times: collar bone broken when born: died of mastoid disease.

VI.77. Willie McC. 1937 - : sclerotics blue: double jointed: no broken bones: healthy child.

Child of V.72.

VI.78. Malcolm W. 1932 - : sclerotics blue: fractured leg three times: looseness of joints: no deafness: parietal, occipital and frontal bossing.

Family G.

IV.14. Samuel McC. 1882 - : sclerotics blue: deafness: tinnitus: may have had fractured hand as a small boy: colour vision normal.

V.87. Sam McC. 1905 - : sclerotics blue: iris blue: fractured skull, wrist and pelvis in accident in 1925: no deafness: no bossing, but head has a square appearance: height 5' 4".

V.88. Mrs. Sam McC. iris brown.

V.89. James McC. 1907 - : sclerotics white: no fractures: no deafness: not examined: information from IV.14.

V.91. Robert McC. 1922 - : sclerotics white: no fractures: no deafness: not examined: information from V.87.

Children of V.87.

VI.79. Samuel McC. 1932 - : sclerotics blue: iris blue: dislocated shoulder aet. 2½: no deafness: no bossing, but head has square appearance (like his father).

VI.80. Catherine McC. 1939 - : sclerotics blue: iris brown: no fractures: no bossing.

IV.16. Mr. B. 1871 - : son of III.3.: colour vision normal.

IV.17. Mrs. B.

V.92. Daughter of IV.16. and 17.

Tables 4 - 8 showing the results of Blood Group and Taste Tests in the Members of Pedigree K .

Table 4 Family A.

Table 5 Family C.

Table 6 Family D.

Table 7 Family E.

Table 8 Families F and G .

No.	Name.	Blood.	Taste.	
			P_2	P_4
IV.1.	Mrs. T.	ON	No	T
IV.2.	Mr. T.	OMN	No	No
V.1.	James T.	ON	No	No
V.5.	William T.	ON	T	T
V.6.	Mrs. Wm. T.	Not bled	No	No
VI.4.	Moira T.	Not bled	No	No
V.8.	Mrs. G.	ON	No	No
VI.7.	James G.	ON	No	T
VI.8.	Elphinstone M.	OMN	No	No
V.10.	John T.	ON	No	T
V.12.	Sam T.	ON	No	T
V.13.	Mrs. Sam T.	BMN	No	T
VI.9.	Andrew T.	BN	No	No
VI.10.	Margaret T.	BMN	No	No
VI.11.	Roland T.	BMN	No	No
VI.12.	Ian T.	BMN	No	T
V.14.	Mrs. F.	ON	No	T
V.15.	Mr. F.	OMN	No	T
VI.13.	Marie F.	ON	No	No
VI.14.	Sarah F.	OMN	No	T
VI.16.	Nan F.	OMN	No	No
V.16.	Alexander T.	OMN	No	T
V.17.	Mrs. Alex. T.	A_1MN	No	T
VI.19.	Marion T.	A_1N	T	T
VI.20.	William T.	OM	No	T
VI.21.	Alexander T.	A_2MN	No	T
VI.22.	Helen T.	A_2N	No	No
V.18.	Andrew T.	ON	No	T
V.19.	Mrs. Andrew T.	BM	No	No
VI.23.	Martha T.	BMN	No	T
VI.24.	Elsie T.	OMN	No	T
VI.25.	Willie T.	OMN	No	T
VI.26.	North T.	OMN	No	T
V.20.	Charles T.	ON	No	T
V.21.	Mrs. Chas. T.	Not bled	No	T
VI.28.	Ella T.	Not bled	No	No
V.22.	Roland T.	ON	No	T
V.23.	North T.	ON	No	T

Family C. Table 5.

No.	Name.	Blood.	Taste. P_2	Taste. P_6
V.30.	William L.	ON	T	T
V.31.	Mrs. Wm. L.	A,M	No	No
VI.29.	Sarah L.	A,MN	No	T
VI.30.	Willie L.	OMN	No	T
VI.33.	Jessie L.	OMN	No	T
VI.34.	Annie L.	Not bled	No	No
V.39.	Mrs. W.	BMN	No	No
V.40.	Mr. W.	BMN	No	T
VI.41.	Sarah W.	BM	No	T
VI.42.	James W.	Not bled	No	T
VI.43.	William W.	Not bled	No	T
V.43.	Robert J.L.	BMN	No	No

Family D. Table 6.

No.	Name.	Blood.	Taste. P_x	Taste. P_6
IV.8.	Mr. C.	A, BMN	No	T
V.47.	Agnes C.	A, BN	No	T
VI.47.	Robert C.	Not bled	No	No
V.49.	Sam C.	BMN	T	T
V.50.	Mrs. Sam C.	OM	T	T
VI.49.	John C.	OM	No	T
VI.50.	Jean C.	BMN	No	No
V.51.	Ina C.	A, N	No	T
V.52.	Willie C.	BN	No	T
V.53.	Mrs. Willie C.	A, N	No	T
VI.55.	James C.	A, BN	No	T
VI.56.	David C.	BN	-	-
V.55.	James C.	A, N	No	T

Family E. Table 7.

No.	Name.	Blood.	Taste. P_3	Taste. P_6
V.57.	Mr. Hugh McC.	BMN	No	No
V.58.	Mrs. Hugh McC.	A, M	No	T
VI.60.	Hugh McC.	BM	No	T
VI.62.	John McC.	A, BMN	No	T
VI.63.	Annie McC.	OMN	No	T
VI.65.	Elizabeth McC.	OMN	No	No
VI.66.	Willie McC.	A, M	No	No
VI.67.	Robert McC.	A, BMN	No	No
V.59.	Willie McC.	OMN	No	T
VI.69.	Ellen McC.	OMN	No	T
V.61.	Mrs. McC.	OMN	T	T
V.62.	Mr. McC.	BM	No	T
VI.71.	Nan McC	OMN	No	No
VI.72.	Rose McC	BMN	No	T
V.63.	Annie McG.	BMN	No	No
V.64.	Thomas McG.	OMN	No	No
V.65.	Fannie McG.	BMN	No	T
V.66.	John McG.	OMN	No	No

Family F. Table 8.

No.	Name.	Blood.	Taste. P_3	Taste. P_4
IV.12.	Mr. McC.	BN	No	No
IV.13.	Mrs. McC.	OM	No	T
V.69.	Mary McC.	OMN	No	T
V.72.	Mrs. W.	OMN	No	T
V.74.	Agnes McC.	OMN	No	T
V.75.	Maria McC.	OMN	No	T
V.76.	Sarah McC.	OMN	No	No
V.78.	Quinton McC.	BMN	No	T
V.80.	Annie McC.	OMN	No	T
V.81.	Margaret McC.	Not bled	No	No
VI.74.	Janet C. (Daughter of V.67.)	A_1MN	No	T

Family G.

IV.14.	Samuel McC.	BN	No	No
V.87.	Mr. Sam McC.	A_2BMN	No	No
V.88.	Mrs. Sam McC.	OMN	No	No
VI.79.	Sam McC.	A_2M	No	No
IV.16.	Mr. B.	ON	No	T
IV.17.	Mrs. B.	OMN	No	T
V.92.	Helen B.	OMN	No	T

(IV.16. is a nephew of III.2.)

PEDIGREE OF COLOUR BLINDNESS, BLUE SCLEROTICS, BRITTLE BONES AND DEAFNESS.

CHART K

EXAMINED	115
NOT EXAMINED	22
DEAD OR ABROAD	71
TOTAL	208
BLOOD GROUP TEST	90
PHENYLTHIO-CARBAMIDE TEST	98

- INFORMATION UNCERTAIN
- BLUE SCLEROTICS 42
- COLOUR BLIND 5+1 6
- BLUE SCLEROTICS AND COLOUR BLIND 3

"History teaches that the commencement of every branch of science is nothing more than a series of observations and experiments which had no obvious connection with one another."

J. von Liebig (1846).

Part IV.

Concerning the Inheritance of Refraction, Ear Lobes and Iris Colour.

During this century a considerable body of knowledge has arisen concerning the inheritance of factors which are not pathological. The outstanding example is the work done upon the blood groups referred to in the previous part. Agglutinins are present in other tissue fluids such as the tears, urine and saliva and it is possible to group patients in this manner. Among the many normal conditions which are known to be mainly, if not exclusively, under hereditary control are the refraction, the condition of the ear lobes and the colour of the iris. The inheritance of myopia is discussed in Part I and it must be remembered that it is possible to work out pedigrees showing the inheritance of all types of refractive error. The aspect of the problems of refraction considered in this part is the hereditary one. Nobody has advocated a bad social environment as a method of reducing hypermetropia.

The inheritance of the ear lobes appears to be controlled by one set of factors. Patients' ear

lobes may be recorded as either attached or free. If the lobule adheres to the side of the head it is recorded as attached : if the lobule is pendant it is recored as free. The statement is made by Baur,Fischer and Lenz (1931) that in certain parts of Germany attached lobes occur in one quarter of the population. I am unaware of any figures applicable to the West of Scotland except those given below. Hilden (1922) has shown with a high degree of probability that attachment or absence of the ear lobe depends upon a recessive factor. Therfore if two parents are recessive all their children will have attached lobes. Homozygous free-lobed individuals, if they marry amongst themselves will only have free lobed children. Heterozygous parents will show a three to one ratio of free and attached lobes. As this condition has got no selective value it would be expected that the majority of people would be heterozygous, and consequently the incidence of attached lobes would be around 25 % .

It is well known that inheritance plays a part in the colour of the iris and a considerable literature exists on the subject. From time to time statements are found in ophthalmological literature regarding both iris colour and refraction which should be capable of

statistical proof. Williamson-Noble (1938) stated "I think there is some association between the inherited colour of the eyes and their inherited refraction. To take a simple case, say the mother is blue-eyed and myopic and the father brown-eyed and hypermetropic, if the child has blue eyes he will probably become a myope, whereas if he has brown eyes he will probably not." I have heard it stated that highly myopic individuals seldom have brown eyes and that glaucoma occurs more frequently in hazel-eyed pepple. Bishop Harman (1913) stated that "Astigmatism should be corrected not only because it accounted for poor vision eye strain and headaches, but because, in many cases, it may be the foster mother of myopia in susceptible subjects." If any of these statements is correct it should be possible to collect data in support.

In the course of routine refraction examination the colour of the iris, refraction, and condition of the ear lobes were recorded in five hundred patients. Pathological cases were excluded and the cases came from Hospital Clinics, School Clinics and private practice. The refractions were classified into two groups, hypermetropes and myopes. Astigmatism was not considered in the classification of this series and the higher plus or minus meridian was takem as the one which determined classification.

The iris colour was classified into three groups brown, heterochrome and blue. Thw brown did not include greenish-brown or hazel and the blue group was strictly limited to grey and blue without any pigment spots visible in the iris stroma. Blue-eyed people with a fringe of brown uveal pigment at the iris margin were classified as blue. The colour standards were based upon Prof.Martin's Augenfarbentafel in which the left hand column was taken as the standard for brown, the right hand column the standard for blue, and the intermediate columns were grouped as representing the heterochrome colours.

The ear lobes were recorded as attached or free. Although numerous gradations were observed between the size of the free lobes and the degree of adhesion of the attached, no great difficulty was found clinically in grouping them as either attached (A) or free (F). In all cases both lobes were examined and one patient, No323 of the series, was observed to have one free lobe and one attached. This was considered to be of sufficient interest to investigate a little more fully and her family history was worked out. This forms Pedigree L and it is described at the end of this section.

It was found that 23 % of the patients had attached ear lobes. This is in keeping with the statement made by Baur, Fischer and Lenz concerning the population in certain parts of Germany which has already been referred to. It is also in keeping with the theoretical 25 % incidence which would be expected on the hypothesis that the condition is due to a single recssive factor which is widely spread in the population. When the figures shown in the tables were submitted to analysis it was found that there was an excess of women with attached ear lobes, greater than should arise by chance. The analysis was carried out by Mr. H.W.Norton at the Galton Laboratory. As far as we knew this sexual difference had not been previously recorded. As it might be due to the racial mixture in the West of Scotland another series of cases was collected in London by Dr. R.R.Race and on analysis the same sexual difference was observed. The whole matter is to be the subject of a joint paper which is in course of preparation.

The incidence of myopia in this series was 21.8 % As the patients were seen primarily because of refractive

errors they are a selected group but the figure is of interest in relation to others which have been published.

Table 9.

Percentage number of cases of myopia in different populations.

	%
Scheerer (Adult see Table 2)	10.2
Riddell (Adult see Table 2)	14.3
Riddell (Children and Adults)	21.8
Brown (Adult see Table 2)	23.8
Bishop Harman (N.O.T.B.Figures 1936)	27.25

The N.O.T.B. figures are based upon 30,000 patients over the age of 16 who were examined by various ophthalmic surgeons for the National Ophthalmic Treatment Board. In spite of the large numbers examined the basis of the figures is a selected group of people who were complaining about their eyes and came under the care of the various surgeons. In my opinion a percentage of 27.25 of myopia is too high an estimate of the incidence in the general population. This forms more evidence for the need of an unselected refraction curve of the population.

The different iris colours varies greatly in European populations and the following table has been constructed from various published sources indicated in the last column.

Table I0.

Percentage Incidence of Blue, Heterochrome and Brown Irides in different European Countries.

		Blue	Heterochrome	Brown	Observer
	Sweden	86.9	8.I	5.0	Lundberg (I922-24).
X	Norway	63.7	22.9	I4.3	Bryn (I929).
	Denmark	26.90	59.I4	I3.96	Eskelund (I938).
	Baden	64.5	27.9	I2.6	Ammon (quoted by Eskelund).
	Italy	I0.3	20.6	69.I	Livi (quoted by Eskelund).
ZZ	England	30.8	55.4	I4.0	Galton (I886).
	Scotland	42.8	48.8	8.4	Riddell (I939).

X Bryn's figures were 63.7 % blue eyes, 22.9 % mixture pale eyes, I2.5 % mixture dark and I.8 % brown eyes. I have added the last two groups together.

ZZ Galton divided the iris colour into eight groups and I have added his groups I and 2 together for blue : 3,4,5 and 6 for heterochrome and 7 and 8 for brown.

Waardenburg (1932) states that in Northern Europe more women than men have non-blue or brown iris colours. He supposes that this fact is dependent upon a dominant sex-linked gene ; a suggestion which was first made by Leng. This view certainly requires confirmation because no dominant sex-linked condition is known to occur in man. If it did so the expected incidence would be twice as many women as men manifesting the gene .

Table II.

Five Hundred Patients classified into Sixteen Groups for the Colour of the Iris. Condition of the Ear Lobes. and the Refraction.

		Iris	
	BR.	Het.	bl.
Ear Lobes Attached	6	65	44
Ear Lobes Free	36	179	170
Refraction Hypermet.	36	198	159
Refraction Myopia	6	48	55

	Hyper.	Myopia
Ear Lobes Attached	89	26
Ear Lobes Free	302	83

Table I2.

One hundred and sixty males under sixteen years of age classified as in Table II. but the figures combined.

	Iris Colour					
	Brown.		Hetero.		Blue.	
	Hm.	My.	Hm.	My.	Hm.	My.
Ear Lobes Attached	2	I	I4	2	6	4
Ear Lobes Free	I6	0	46	I2	40	8

Table I3.

One hundred and thirteen males over sixteen years of age classified in a similar manner to Table I2.

	Iris Colour					
	Brown.		Hetero.		Blue	
	Hm.	My.	Hm.	My.	Hm.	My.
Ear Lobes Attached	I	0	8	I	7	4
Ear Lobes Free	2	I	37	7	32	I3

Table I4.

One hundred and nineteen females under sixteen years of age classified in a similar manner to the males in the previous tables

		Iris Colour					
		Brown.		Hetero.		Blue.	
		Hm.	Mv.	Hm.	Mv.	Hm.	Mv.
Ear Lobes	Attached	I	0	I3	3	II	I
	Free	9	I	28	9	32	II

Table I5.

One hundred and eight females over sixteen years of age classified in a similar manner to Table I4.

		Iris Colour					
		Brown.		Hetero.		Blue	
		Hm.	Mv.	Hm.	Mv.	Hm.	Mv.
Ear Lobes	Attached	I	0	20	4	5	6
	Free	4	3	30	I0	I7	8

The actual data upon which these figures are based are placed in Appendix 3.

As stated above these tables were submitted to statistical analysis by Mr.H.W.Norton at the Galton Laboratory and I am indebted to him for the following details. It was possible to work out whether Dr. Race in his London series of Ear Lobes observed the same proportion of individuals with attached lobes and the answer was in the negative, p = 0.032 or one chance in thirty that the difference was due to random sampling. This of course may be due to differences in the population of London and Glasgow. Dr. Race and myself have since had an opportunity of working out a series together. This experiment was done under Mr. Norton's supervision and we reached almost complete agreement in our results, differing in one case out of eighty. This difference had no effect on the validity of the test of association between sex and attachment referred to above, as long as the figures are examined to see whether that association differs between the two sets of data.

As the data stand eye colour is not satisfactorily accounted for by the hypothesis of a single gene substitution, p = 0.022 or about one in fifty. The deviations from expectation are not very high, in the sense that a rather small proportion of errors of classification

would account for them. If it assumed that the blues are correctly classified, and that errors occur in distinguishing brown from heterochrome, the expected number of browns in 500 is about 60 and only 42 were observed (see Table II). This may be due to a too critical standard in assessing the purity of brown . When the segregation is studied separately for the four groups formed by dividing the data by sex and by ear lobe attachment, the principal part of the deviation from the single gene hypothesis arises from the females with the attached lobes. The other three groups also show deviations in the same direction One possibility is that somatic mutation may cause brown eyes to be flecked with yellow pigment and so become classified as heterochrome. The data do not contradict such a supposition. The reverse somatic mutation could also occur, but would not be obvious in the data because the blues and heterochromes are so common relatively. This matter can only be decided by collecting data based upon a wider classification of iris colour, grouping the cases into the sixteen divisions of Prof. Martin's Augenfarbentafel and testing the data,arranged into various groups, against a single gene hypothesis. Work on these lines is being carried out, with the co-operation of Prof. R.A.Fisher.

Pedigree L.

A Pedigree of Normal Individuals Segregating for Four Hereditary Factors.

The members of this family were investigated for refraction, iris colour, condition of the ear lobes and ability to taste phenyl-thio-carbamide. The reason for this investigation was the discovery of a woman with one attached lobe and one free lobe in the series already discussed. She could taste P.T.C. and was a hypermtropic brown eyed individual with one attached ear lobe and one free (I.4).

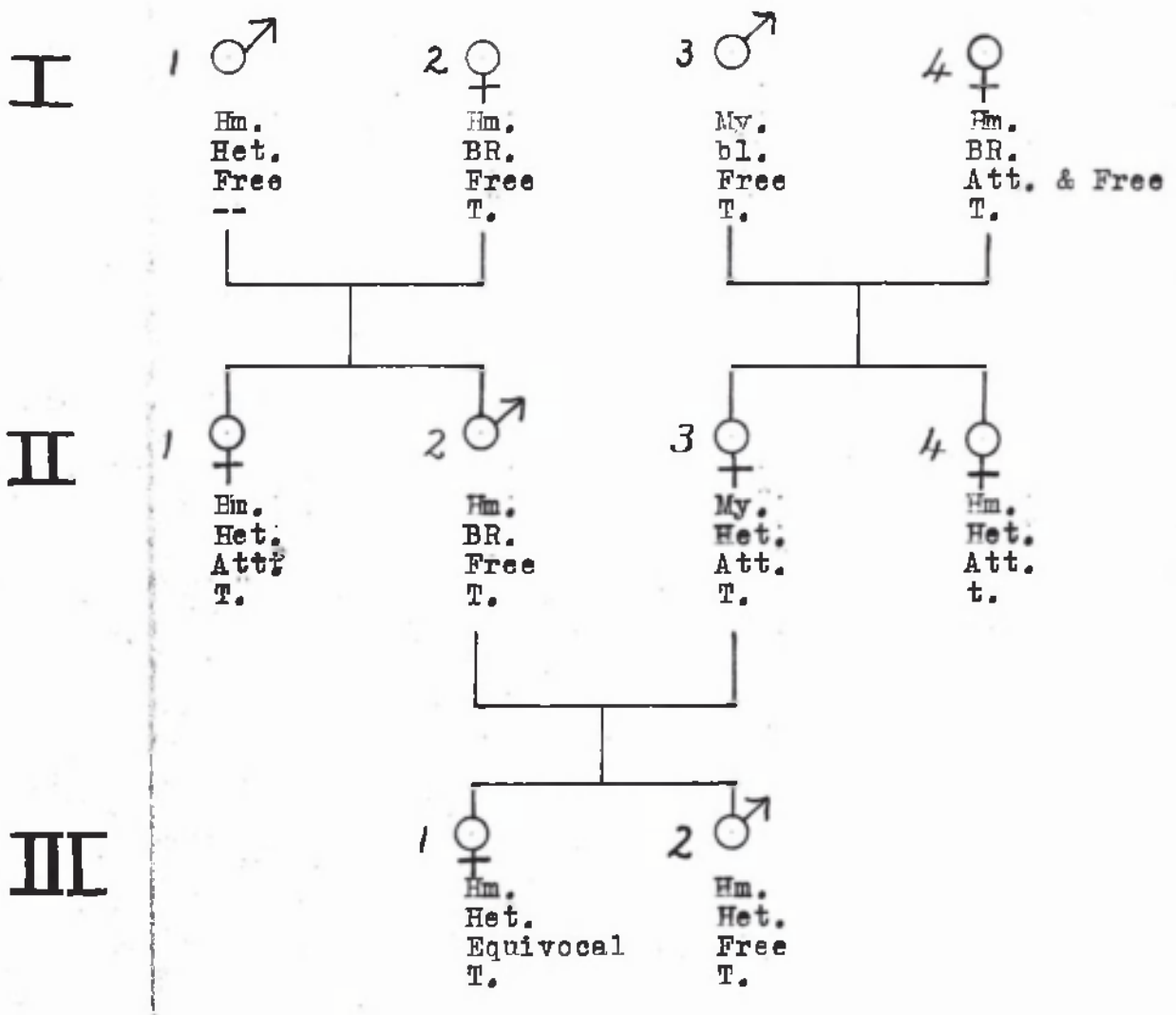
Her husband, I.3, was a blue eyed myopic free-lobed man who could also taste P.T.C. Of the two daughters examined one, II 3, was a myope with attached lobes, heterochromic irides and a taster. The other, II 4, was a hypermetropic, heterochromatic, attached lobe, non-taster. From this it follows that either or both I.3 & 4 were heterozygous for the factor controlling the ability to taste P.T.C.

II.3 was married to a brown-eyed, hypermetropic man who was a taster. They had two children III.1 & 2. Both the children were hypermetropic, heterochromatic tasters. The small girl's ears were equivocal but the boy's ears were free. It follows that II.2 is probably heterozygous for ear lobes if it is found that

III. I is still attached when she gets older. The reason why she is recorded at present as equivocal is because she is at present five years old and if the lobes develop more she will be free, but at present she is doubtfully attached. II.2 had a sister who was definitely attached, a hypermetrope and a taster. The parents of II.I and 2 were both hypermetropes with free ear lobes. Again one at least must have been heterozygous for this factor. I.I had heterochromic irides whilst I.2 had brown ones. As I.I was dead no record of tasting could be obtained and the ear lobes were confirmed by photographs. The two children (II. I & 2) and his wife I.2 were quite definite about the colour of his eyes : they were "greeny-brown".

CHART L

PEDIGREE SHOWING SEGREGATION OF FOUR HEREDITARY FACTORS.



Refraction - Hm.-Hypermetropia, My.- Myopia.

IrisColour - BR.-Brown, Het.- Heterochrome. bl.- Blue.

Ear Lobes - Att.-Attached - Free Lobes.

Phenyl-thio-carbamide - T- Taster t - non-taster.

Hitherto Unpublished.

A Concluding Note on Problems of Human Heredity.

The previous sections contain several examples of the material which a clinical ophthalmologist may ~~may~~ submit to geneticists for further study. Progress can only be made by the closest co-operation between the workers concerned. It is becoming increasingly difficult for workers in one side of a field to know what is going on at the other side. The details demanded for linkage studies in man are of such a kind that it is impossible to work out a pedigree in the course of routine work in a clinic. The information required in many cases cannot be produced from hospital work at all ; for example the figures needed to construct a normal refraction curve of the population could only be got from samples not attending an eye clinic and at the same time can only be collected by a skilled refractionist. A positive request such as that made by Dr. Bell and Prof. Haldane to me for a search of haemophilic pedigrees containing colour-blind individuals, can be carried out with the help of various colleagues, but even in this case considerable negative information had to be sifted out.

I am a little doubtful if many pedigrees such as Pedigree K in this thesis, can be worked out for non-pathological factors such as blood groups and taste tests in existing circumstances. Data of this type take a great deal of time and labour to collect and considerable tact is required in getting non-affected members of the families to co-operate.

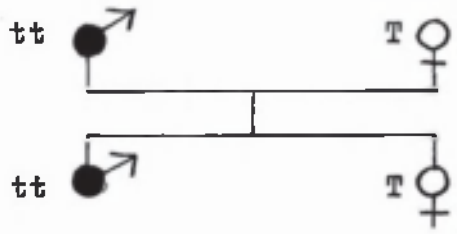
From the genetic standpoint difficulties arise from the small size of the human family and the incomplete knowledge as to the type of mating, e.g. whether the parents are homozygous or heterozygous for the factor concerned. This aspect of the matter is discussed by Mather (1938) in his book on the measurement of linkage in heredity. He also indicated to those ignorant of mathematics, the extreme complexity of the methods required in the analysis of such material. The methods employed are essentially the same as those used in other branches of genetics but they are more complex and often less efficient because of the shortcomings of the human data available. Present progress in our knowledge of human genetics is largely

due to the work of Prof.R.A.Fisher who has developed the statistical methods required for its analysis. These methods are described in two standard books which he has written on the subject of statistical methods and on the design of experiments, as well as numerous papers concerning linkage in human pedigrees (Fisher 1934, 1935a, 1935b, 1936, 1937, 1938.). Fisher points out in one of his papers that collectors of human pedigrees in the past had no knowledge of the many purposes to which their material is now being put. Facts which are now known to have value were frequently omitted, e.g. the sex of normal children, the exact birth order and so on.

In human linkage studies a large amount of material does not give any evidence because the matings are not suitable. This does not mean of course that such families should not be placed on record, but for the application of linkage formulae they are rejected. Figures 3, 4, and 5 illustrate this matter. They are taken from a paper by Fisher (1935a) on the detection of linkage with dominant abnormalities, the object being to find out whether or not any linkage existed

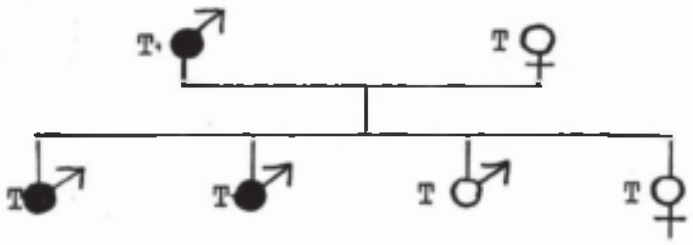
between the gene concerned with the production of the abnormality and the gene concerned with the ability to taste phenyl-thio-carbamide.

Figure 3.



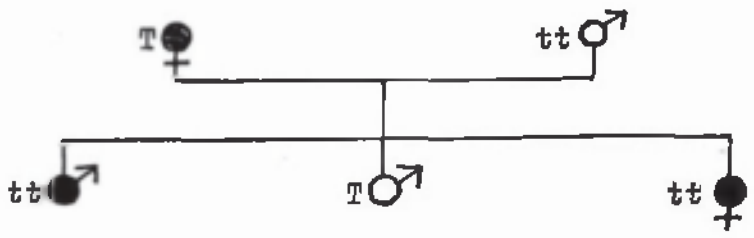
A family of this type is rejected owing to the affected parent being a non-taster and therefore homozygous.

Figure 4.



A family of the type rejected owing to the absence of any non-tasting child.

Figure 5.



A family which supplies information as to linkage ; since the normal parent is a non-taster. The affected parent must be heterozygous for the dominant defect because she has a normal child. She must also be heterozygous for T-factor because she has two non-tasting children.

It is possible to detect that a gene responsible for a significant amount of variation in a graded character such as stature or eye colour is linked genetically to another gene. This second gene may be responsible for significant variations in another graded character or it may be in one whose behaviour is precisely known. By such analysis the detection of linkage might serve to identify genes whose presence was unsuspected (Penrose 1938).

The technical details of such calculations are beyond the range of an ordinary clinical worker, but it is of importance to remember that such calculations

are dependent for their accuracy upon observed clinical data. If the observations provided by the clinical investigator are inaccurate or lacking in obtainable information, no amount of statistical skill will add to our knowledge.

In the first part of this thesis myopia, night-blindness and retinitis pigmentosa are discussed with illustrative family histories; it ends with an account of a pedigree in which all three conditions are present.

In the second part the linkage which was established between haemophilia and colour-blindness by Dr. Julia Bell and Prof. J.B.S.Haldane is described. It includes two pedigrees containing both conditions which were worked out by myself. This is an example of co-operation between scientific and clinical workers leading to an advance in knowledge.

In the third part an account of three pedigrees of blue sclerotics is given. Two were investigated prior to 1931, the year in which Bernstein first demonstrated the possibility of calculating linkage values in man. The third blue sclerotic pedigree

was investigated for other factors, those controlling colour-blindness, blood groups and the ability to taste phenyl-thio-carbamide. The object in doing this was to provide material for further linkage studies. No such genetic association was found.

The fourth part concerns the inheritance of normal factors involved in the refraction of the eye, the colour of the iris and the condition of the lobes of the ears. No association between the iris colour and state of the refraction was found in a series of five hundred consecutive cases. An unexplained excess of females with attached ear lobes was observed. As far as I am aware this had not been observed before, but was confirmed by a series observed by another worker. The manner in which such normal conditions are transmitted may act as markers for further studies in genetic linkage.

It is apparent that further progress in this complex field can only be made by the closest co-operation between clinicians, geneticists and statisticians. No single individual can grasp all the technical details involved, but ophthalmologists have much to contribute to such studies.

The critical collection of data will lead to progress and in this clinicians have a most important part to play by keeping a constant watch for cases in which fuller investigation will add to knowledge. Certain examples may be drawn from what has been written above. The examination of haemophilics and their unaffected male relatives for colour defects is one obvious step. The further study of refractive errors from the hereditary and genetic aspect is required. Many problems have not been mentioned at all.

"For I believe that, while theories are tfansitory, a record of facts has a permanent value" is the motto placed at the beginning of this thesis. Ophthalmologists are in a unique position to carry this out in practice.

Appendices.

I. $Y = B X^{-\alpha}$

2. Addendum to Pedigree H by Prof, J.B.S, Haldane.

3. Data concerning the Refraction, Ear Lobes and Iris Colour in Five Hundred Patients.

Appendix I.

$y = bx^{\alpha}$

Genes often affect the speed at which processes take place in the body. As an organism grows certain relations are maintained between the sizes of its parts. A study of their components throws further light upon the operation of the genes which influence them.

Suppose y is the size of a particular organ, and x that of the rest of the body, minus the organ in question. Then the relation of the organ to the body throughout growth is given by the formula : $y = bx^{\alpha}$ in which b and α are constants. The term b merely expresses the intitial relationship ; that is to say, the value of y when $x = I$. However, that of the exponent is of great interest. When $\alpha = I$, the size of the organ remains the same relative to that of the body. When $\alpha > I$ it increases, and when $\alpha < I$ it diminishes. If the value of α is much above or below unity, a given increase in the size of the body produces a very disproportionate change in that of the organ. Genes may influence one or other of these components. These relations have been analysed by J.S.Huxley (1932) and this account of the matter is taken from Ford (1938).

Appendix 2.

Addendum to Pedigree H. by Prof.J.B.S.Haldane (previously published in the Jl.Genetics 1938.XXXVI.45-51).

Bell and Haldane (1937) on the basis of six pedigrees, one of which was supplied by Dr. Riddell, concluded that linkage between the genes for colour-blindness and haemophilia was conclusively demonstrated, and gave a very rough estimate of 5 % for the frequency of crossing-over. The present pedigree, though it would furnish little or no evidence of linkage if taken by itself, adds something to that of the others.

The only woman who certainly is or was doubly heterozygous is IV.14. She certainly received the gene for haemophilia from her father, III.8, and is certainly heterozygous for colour-blindness, since she bore a colour-blind son. She cannot be homozygous, as she is not colour-blind. There can be no reasonable doubt that she received the gene for colour-blindness from her mother III. 7 ,who had a colour-blind father and son. The alternative would be that III.8 was a deuteranope. The a priori probability of this is 0.014, and this is greatly reduced by two facts. III.8 was a jeweller, and colour-blindness

would have interfered with his trade. And this defect, had it existed, would have been noticed in a family where colour-blindness was already familiar.

We conclude that IV.14 is $\frac{C +}{+ H}$ in the terminology of Bell and Haldane, that is to say, carried the genes for colour-blindness and haemophilia in opposite chromosomes, or in other words in repulsion. If x is the frequency of crossing-over between these genes, the probability that V.13, who is not a haemophilic, should be colour-blind is I - x.

Given our knowledge of her three sons, it is almost certain that IV.11 is $\frac{+ +}{+ H}$. The probability that she is $\frac{C +}{+ H}$ is about $x^2(I - x)$ or 0.002, which may be neglected. However, if VI.3 turns out to be colour-blind some more information on linkage will be available (he is still too young to examine - W.J.B.R.1939).

If we combine these data with those collected by Bell and Haldane we find $P(\frac{1}{2}.p) = 3.9 \times 10^{-7}$. That is to say, the probability that the total of the observed results should be due to chance is reduced to half its former value, and the odds are now 2½ millions to one against this explanation.

Bell and Haldane calculated a probability $P(x,p)$ that the observed results should be obtained if x is the frequency of crossing-over and p the frequency of deuteranopia in the male population. The leading term of $P(x,p)$ is now $x(1-x)^{28.75}$. Thus the maximum likelihood estimate of x is reduced from 3.5 to 3.3 %, the mean from 6.7 to 6.3 % and the median from 5.7 to 5.5 % .

When allowance is made for a plausable a priori probability distribution of cross-over values as described by Bell and Haldane, the conclusion is reached that the true cross-over frequency is as likely to be above as below 4.5 %.

It is only by the patient accumulation of numerous pedigrees such as this that the linkage value will be finally established.

Summary.

A family is described in which one woman is heterozygous both for haemophilia and colour-blindness, these being derived from different parents. Her only son does not show crossing-over.

Appendix 3.

Data concerning the Ear Lobes, Refraction and Iris Colour of Five Hundred Consecutive Patients in whom these points were recorded.

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.	
I	F	I0	A	Het.	+2.0	+2.0	+5.0	+5.0	Hm.
2	F	9	F	Het.	+3.5	+3.0	+3.5	+3.0	Hm.
3	M	7	A	Het.	−I.25	−I.25	−I.25	−I.25	My.
4	M	8	F	bl	+2.5	+2.5	+2.5	+2.5	Hm.
5	M	8	A	BR	+4.5	+I.0	+4.5	+I.0	Hm.
6	M	9	F	bl	+4.0	+4.0	+4.0	+4.0	HM.
7	F	I3	F	bl	+2.0	+2.0	+2.0	+2.0	Hm.
8	F	8	F	Het.	+3.5	+3.5	+3.5	+3.5	Hm.
9	M	6	F	bl	+8.0	+7.0	+8.0	+7.0	Hm.
I0	M	I0	F	bl	+I.5	+I.5	+I.5	+I.5	Hm.
II	F	I0	F	BR	+I.25	+I.25	+I.25	+I.25	Hm.
I2	M	5	A	Het.	+4.5	+4.5	+5.5	+5.5	Hm.
I3	F	8	A	bl	+5.0	+3.5	+5.0	+3.5	Hm.
I4	M	40	F	BR	+I.5	+I.0	+I.5	+I.0	Hm.
I5	F	56	F	Het.	+2.0	+2.0	+2.0	+2.0	Hm.
I6	F	30	A	Het.	+I.5	+I.5	+I.5	+I.5	Hm.
I7	M	I5	F	Het.	−2.0	−2.0	−2.0	−2.0	My.
I8	M	40	A	Het.	+3.0	+3.0	+3.0	+3.0	Hm.
I9	M	65	F	bl	+3.5	+3.5	+3.5	+3.5	Hm.
20	F	64	F	BR	+I.0	+I.5	+I.25	+I.25	Hm.
2I	F	44	A	Het.	−2.5	−3.5	−2.5	−5.5	My.
22	F	37	A	Het.	+7.0	+6.0	+4.0	+4.0	Hm.
23	F	69	F	bl	−2.0	−2.0	−2.0	−2.0	My.
24	M	8	F	bl	+8.5	+7.0	+8.5	+7.0	Hm.
25	F	I4	F	bl	−5.0	−8.0	−3.5	−3.5	My.

Case No.	Sex	Age	Ear	Iris	Right		Left		
					Hor.	Vert.	Hor.	Vert.	
26	F	I3	F	Het.	−0.75	−0.75	−2.0	−2.0	My.
27	M	I3	F	BR	+2.0	+2.0	+2.5	+2.5	Hm.
28	M	I3	F	Het.	+6.0	+7.0	+6.0	+7.0	Hm.
29	M	9	F	bl	+9.0	+7.0	+9.0	+7.0	Hm.
30	M	I2	F	bl	+6.0	+4.0	+6.0	+4.0	Hm.
3I	F	I3	F	bl	−3.5	−0.5	−3.5	−0.5	My.
32	M	57	F	Het.	+I.5	+I.5	+I.5	+I.5	Hm.
33	M	60	F	bl	−0.5	−0.5	−0.5	−0.5	My.
34	M	65	A	bl	+2.5	+3.5	+2.5	+3.5	Hm.
35	M	52	F	Het.	+I.0	+I.0	+I.0	+I.0	Hm.
36	F	2I	A	Het.	+3.0	+4.0	+6.0	+8.0	Hm.
37	M	5I	F	bl	+0.75	+0.75	+0.75	+0.75	Hm.
38	M	67	F	bl	+3.0	+3.0	+3.0	+3.0	Hm.
39	M	62	F	Het.	+I.0	+2.0	+I.0	+2.0	Hm.
40	M	47	F	Het.	+5.0	+5.0	+5.0	+5.0	Hm.
4I	M	2I	A	Het.	+5.0	+5.0	+6.0	+3.5	Hm.Ob.
42	M	5	F	bl	−8.0	−8.0	−8.0	−8.0	My.
43	F	9	F	Het.	+3.5	+4.5	+3.5	+4.0	Hm.
44	F	9	F	Het.	+2.75	+2.75	+2.75	+2.75	Hm.
45	F	I3	A	Het.	+2.5	+2.5	+2.5	+2.5	Hm.
46	F	9	F	bl	+2.75	+2.75	+2.75	+2.75	Hm.
47	M	9	F	Het.	+I.5	−2.0	+2.0	−2.0	MyOb.
48	F	9	F	Het.	+7.0	+7.0	+7.0	+7.0	Hm.
49	F	7	F	bl	−2.0	−3.25	−2.0	−3.25	My.
50	F	I0	F	bl	+5.5	+3.25	+5.5	+3.25	Hm.Ob.

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.	
5I.	M	44	F	bl	−0.75	−0.75	−0.75	−0.75	My.
52.	M	35	F	Het.	+I.0	+I.0	+I.0	+I.0	Hm.
53.	F	55	A	Het.	+3.5	+ 4.0	+ 4.5	+4.5	Hm.
54.	F	64	F	bl	+I.0	+I.0	+I.0	+I.0	Hm.
55.	M	68	F	Het.	+2.75	+2.75	+2.75	+2.75	Hm.
56.	M	56	F	Het.	+2.0	+2.0	+2.0	+2.0	Hm.
57.	F	71	F	Het.	+2.5	+2.5	+2.5	+2.5	Hm.
58.	F	60	A	Het.	+2.5	+2.0	+2.5	+2.0	Hm.
59.	F	55	A	Het.	−14.0	−14.0	−12.0	−12.0	My.
60.	F	6	F	bl	+3.0	+3.0	+2.0	+2.0	Hm.
6I.	F	26	F	Het.	+I.0	+3.0	+4.0	+5.0	Hm.
62.	F	18	F	BR	+8.0	+5.0	+7.0	+5.0	Hm.
63.	M	9	F	bl	+7.0	+6.0	+3.5	+3.5	Hm.Ob.
64.	M	7	F	Het.	+6.0	+2.5	+6.0	+2.5	Hm.Ob.
65.	F	8	F	BR	+3.0	+3.0	+3.0	+3.0	Hm.
66.	F	9	F	Het.	+2.0	+2.0	+3.0	+2.0	Hm.
67.	M	6	F	Het.	−I.5	−I.5	−I.5	−I.5	My.
68.	M	9	A	Het.	+7.0	+8.0	+7.0	+8.0	Hm.
69.	M	8	F	bl	+5.5	+2.5	+5.5	+2.5	Hm.
70.	F	7	F	bl	+I0.0	+8.0	+I0.0	+8.0	Hm.
7I.	M	11	F	BR	+2.5	+2.5	+2.5	+2.5	Hm.
72.	F	5	F	bl	+4.0	+4.0	+4.0	+4.0	Hm.
73.	F	10	F	bl	−I.25	−I.25	−I.25	−I.25	My.
74.	F	33	A	Het.	+3.0	+I.5	+5.0	+I.5	Hm.
75.	F	28	A	bl	−14.0	−14.0	−14.0	−14.0	My.

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.	
76.	F	77	A	Het.	+3.5	+3.5	+3.5	+3.5	Hm.
77.	M	11	F	Het.	+5.5	+2.0	+5.5	+1.5	Hm.Ob.
78.	F	5	F	BR	+4.0	+1.5	-13.0	-13.0	My.
79.	F	13	F	Het	+7.0	+7.0	+6.0	+6.0	Hm.
80.	M	12	F	Het	-0.75	-0.75	-0.75	-0.75	My.
81.	M	6	F	bl	+3.5	-1.0	+3.5	-1.0	My.
82.	M	7	F	BR	+4.5	+4.5	+4.5	+4.5	Hm.
83.	F	9	A	bl	+3.0	-1.0	+3.0	-1.0	My.
84.	M	13	F	Het	+3.5	+3.5	+6.0	+2.0	Hm.
85.	M	9	F	Het	+6.5	+5.0	+6.5	+5.0	Hm.
86.	M	12	F	bl	-5.0	-8.0	-1.5	-2.5	My.Ob.
87.	M	10	F	Het	+5.0	+5.0	+5.0	+5.0	Hm.
88.	M	5	F	Het	+3.5	+3.5	+3.5	+3.5	Hm.
89.	M	35	A	bl	+2.5	+0.5	+2.5	+0.5	Hm.
90.	M	62	A	BR	+1.0	+1.0	+0.5	+0.5	Hm.
91.	F	21	A	Het	+1.5	+1.0	+1.5	+0.5	Hm.
92.	M	39	F	bl	-14.0	-I^{8}.0	-14.0	-I^{8}.0	My.
93.	F	21	F	bl	-2.0	-2.0	-2.0	-2.0	My.
94.	M	55	F	bl	+0.75	+0.75	+0.75	+0.75	Hm.
95.	M	70	F	bl	+3.5	+3.5	+3.5	+3.5	Hm.
96.	F	11	F	bl	+3.0	+3.0	+1.5	+1.5	Hm.
97.	M	9	A	Het	+6.5	+4.5	+4.5	+4.5	Hm.Ob.
98.	F	11	F	bl	+4.0	+4.0	+4.0	+4.0	Hm.
99.	F	6	F	Het	+4.5	+3.5	+3.0	+3.0	Hm.
100.	M	6	F	BR	+6.5	+2.0	+2.0	+6.5	Hm.Ob.

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
101.	M	8	F	bl	Hm.Ob	+6.5	+2.5	+2.5	+5.0
102.	M	5	F	bl	My.	-11.0	-11.0	-11.0	-11.0
103.	M	14	F	bl	Hm.	+18.0	+9.0	+9.0	+10.5
104.	M	10	F	Het	Hm.	+5.5	+3.5	+5.5	+3.5
105.	M	8	F	BR	Hm.	+4.5	+3.5	+4.5	+3.5
106.	F	11	F	bl	Hm.Ob	+4.0	+0.5	+4.0	+0.5
107.	M	9	F	Het	My.	-5.0	-5.0	-10.0	-10.0
108.	M	45	F	bl	My.	-24.0	-24.0	-22.0	-22.0
109.	M	39	F	Het	Hm.Ob.	+1.5	+1.5	+2.0	+3.0
110.	F	66	F	Het	My.	-14.0	-14.0	-2.0	-1.0
111.	F	5	F	bl	Hm.	+1.5	+1.5	+1.5	+1.5
112.	M	10	F	bl	Hm.	+7.0	+7.0	+6.0	+6.0
113.	F	10	F	bl	My.Ob	+1.5	-2.0	+0.75	+0.75
114.	M	7	F	BR	Hm.	+4.5	+4.5	+7.0	+7.0
115.	M	5	F	bl	Hm.	+4.5	+4.5	+5.5	+5.5
116.	F	5	F	bl	Hm.	+8.0	+7.0	+8.0	+7.0
117.	F	11	F	Het	Hm.	+1.0	+1.0	+1.0	+1.0
118.	M	11	F	bl	Hm.	+4.5	+4.5	+4.5	+4.5
119.	M	5	F	bl	Hm.	+7.0	+7.0	+7.0	+7.0
120.	M	72	F	Het	Hm.	+1.5	+1.5	+1.5	+1.5
121.	M	57	F	Het	Hm.	+1.75	+1.75	+1.5	+1.5
122.	M	61	F	Het	Hm.	+4.0	+3.5	+4.0	+3.5
123.	M	32	F	Het	My.	±0.25	±0.25	±0.25	±0.25
124.	F	46	A	Het	Hm.	+1.5	+1.5	+1.0	+1.0
125.	M	48	F	bl	Hm.	+2.0	+2.0	+3.0	+3.0

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
I26.	M	41	F	bl	Hm.	+I.0	+I.0	+2.0	+2.0
I27.	F	48	F	Het	Hm.Ob.	+4.0	+I.0	+2.5	+5.0
I28.	F	10	A	Het	Hm.Ob.	+5.0	+3.5	+2.5	+5.0
I29.	F	12	F	Het	Hm.	+I.25	+I.25	+I.25	+I.25
I30.	F	9	A	Het	Hm.	+I.5	+I.5	+I.5	+I.5
I3I.	F	38	A	bl	Hm.	+I.25	+I.25	+I.25	+I.25
I32.	M	32	F	Het	Hm.Ob.	+7.0	+4.0	+3.0	+5.0
I33.	M	73	F	bl	My.	−I.0	−2.0	−7.0	−9.0
I34.	F	16	F	BR	My.	−7.0	−8.0	−6.0	−9.0
I35.	M	35	F	BR	My.	−4.5	−4.5	−6.0	−7.0
I36.	F	45	F	BR	My.Ob.	−9.0	−I2.0	−9.0	−I2.0
I37.	F	10	F	Het	Hm.	+I.5	+I.5	+I.5	+I.5
I38.	M	16	A	bl	My.	−I.25	−I.25	−I.0	−I.0
I39.	M	16	F	Het	My.	−3.0	−0.75	−9.0	−9.0
I40.	F	7	F	bl	Hm.	+7.0	+7.0	+7.0	+7.0
I4I.	F	8	A	bl	Hm.	+II.0	+6.0	+I2.0	+8.0
I42.	F	11	F	Het	My.	−6.0	−6.0	−6.0	−6.0
I43.	F	10	F	bl	Hm.	+8.0	+7.0	+7.0	+6.0
I44.	M	67	F	bl	Hm.	+I.5	+I.5	+I.5	+I.5
I45.	M	12	F	Het	Hm.	+3.0	+I.5	+3.0	+I.5
I46.	F	9	F	bl	My.	−2.0	−4.0	−3.0	−6.0
I47.	M	5	A	Het	Hm.	+5.0	+5.0	+5.0	+5.0
I48.	F	64	F	Het	Hm.	+I.75	+I.75	+I.75	+I.75
I49.	F	41	F	Het	My.Ob.	−2.0	−0.5	−0.5	−2.0
I50.	F	20	F	bl	Hm.	+I.5	+I.5	+I.5	+I.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
151.	M	56	F	Het	Hm.	+I.5	+I.5	+I.0	+I.0
152.	M	53	F	Het	Hm.Ob.	+I.5	+I.5	+2.5	+I.5
153.	M	52	F	Het	Hm.	+2.0	+2.0	+2.0	+2.0
154.	F	23	F	bl	Hm.	+I.75	+I.75	+I.75	+I.75
155.	F	12	F	BR	Hm.	+2.0	+2.0	+2.0	+2.0
156.	M	8	F	Het	My.	−I.5	−I.5	−I.5	−I.5
157.	F	5	A	bl	Hm.	+8.0	+8.0	+8.0	+8.0
158.	M	10	F	BR	Hm	+I.5	+I.5	+I.5	+I.5
159.	F	13	F	Het	Hm.	+5.0	+3.0	+5.0	+2.0
160.	M	8	F	bl	Hm.	+6.0	+4.0	+6.0	+4.0
161.	F	9	A	Het	Hm.	+I.5	+I.5	+I.5	+I.5
162.	M	13	F	Het	Hm.	+3.0	+3.0	+3.0	+3.0
163.	M	6	F	BR	Hm.	+I.5	+I.5	+I.5	+I.5
164.	F	42	F	Het	Hm.	+6.0	+2.5	+6.0	+2.5
165.	M	10	F	bl	My.	−I.0	−I.0	−I.0	−I.0
166.	F	22	F	bl	My.	−4.5	−4.5	−3.5	−5.0
167.	F	17	F	bl	My.	−4.0	−4.0	−4.0	−4.0
168.	M	8	F	Het	Hm.	+I.0	+I.0	+I.0	+I.0
169.	M	11	A	bl	My.	−I.5	−I.5	−I.5	−I.5
170.	M	5	F	Het	Hm.	+3.0	+3.0	+4.0	+4.0
171.	M	6	F	BR	Hm.	+2.5	+2.5	+4.5	+3.0
172.	M	10	F	Het	Hm.	+7.0	+5.0	+7.0	+5.0
173.	M	12	F	bl	Hm.	+5.0	+5.0	+9.0	+9.0
174.	M	8	A	bl	Hm.	+9.0	+8.0	+9.0	+8.0
175.	M	5	F	bl	Hm.	+5.0	+4.5	+5.0	+4.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
176.	M	7	F	Het	Hm.	+6.0	+6.0	+7.0	+7.0
177.	F	5	A	bl	Hm.	+8.0	+8.0	+8.0	+8.0
178.	F	50	F	Het	Hm.	+I.5	+I.5	+I.5	+I.5
179.	M	73	F	bl	Hm.	+ I.5	+I.5	+I.5	+ I.5
180.	M	52	F	Het	My.	−I.0	−I.0	−I.0	−I.0
181.	F	13	F	Het	Hm.	+8.0	+3.0	+2.5	+2.5
182.	M	7	F	Het	Hm.	+ 4.0	+4.0	+6.0	+6.0
183.	M	10	F	Het	Hm.	+ 4.0	+3.0	+5.0	+4.0
184.	F	7	A	Het	Hm.	+ 4.0	+ 4.0	+4.0	+4.0
185.	F	7	F	bl	Hm.	+ 2.5	+ 2.5	+2.5	+2.5
186.	M	19	F	bl	My.	− I.0	−I.0	−0.75	−0.75
187.	M	74	F	bl	Hm.	+ 2.5	+ 2.5	+2.5	+2.5
188.	M	41	F	bl	My.	−I.25	− 0.75	−I.0	− 0.75
189.	F	48	F	Het	Hm.	+2.0	+2.0	+2.0	+2.0
190.	M	13	F	Het	Hm.	+5.5	+4.5	+9.0	+7.0
191.	F	13	F	Het	Hm.	+7.0	+7.0	+7.0	+7.0
192.	F	13	F	Het	Hm.	+4.5	+4.5	+6.0	+5.5
193.	F	12	F	Het	Hm.	+8.0	+6.5	+8.0	+6.5
194.	F	7	F	Het	Hm.	+ 3.5	+ 3.5	+3.5	+3.5
195	M	13	F	Het	My.	− 3.0	−2.0	−3.0	−2.0
196.	M	8	A	Het	Hm.	+ 8.0	+ 8.0	+8.0	+8.0
197.	F	48	F	bl	Hm.	+I.25	+I.25	+I.25	+I.25
198.	M	47	A	Het	Hm.	+I.25	+I.25	+5.0	+7.0
199.	M	32	A	bl	My.Ob.	+4.0	− 0.5	+4.0	− 0.5
200.	F	26	A	bl	Hm.	+I.5	+I.5	+I.5	+I.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
201.	M	38	A	bl	Hm.	+3.5	+3.5	+3.5	+3.5
202.	M	18	F	bl	My.	+3.5	−0.5	+3.5	−0.5
203.	M	66	F	bl	My.	−0.5	−0.5	−0.5	−0.5
204.	M	52	F	Het	My.	−2.0	−3.5	−2.0	−4.0
205.	F	50	F	Het	Hm.	+4.0	+4.0	+4.0	+4.0
206.	M	42	A	bl	My.	+1.5	−0.5	+2.0	−1.0
207.	F	68	F	Het	Hm.	+2.25	+1.25	+2.5	+1.5
208.	F	29	A	bl	Hm.	+4.0	+4.0	+4.0	+4.0
209.	F	35	A	bl	Hm.	+3.0	+3.0	+3.0	+3.0
210.	F	22	A	bl	My.	−1.0	−1.0	−1.0	−1.0
211.	F	74	F	bl	Hm.	+3.0	+3.0	+3.0	+3.0
212.	M	18	F	bl	Hm.	+1.5	+1.5	+1.5	+1.5
213.	F	9	A	Het	Hm.	+1.25	+1.25	+1.25	+1.25
214.	M	16	F	bl	Hm.	+5.0	+5.0	+4.0	+4.0
215.	M	48	A	bl	Hm.	+3.0	+3.0	+2.5	+2.5
216.	M	68	F	bl	My.	−0.5	−0.5	−0.5	−0.5
217.	F	23	F	bl	Hm.	+3.5	+3.5	+4.5	+3.5
218.	F	68	F	bl	My.	−3.0	−3.0	−1.0	−1.0
219.	M	69	F	bl	Hm.	+3.5	+3.5	+3.5	+3.5
220.	M	57	F	Het	Hm.	+1.5	+1.5	+1.5	+1.5
221.	M	68	F	Het	Hm.	+5.0	+5.0	+5.0	+5.0
222.	M	58	F	bl	Hm.	+1.5	+1.5	+1.5	+1.5
223.	M	57	F	Het	Hm.Ob	+1.5	+1.0	+2.5	+2.0
224.	M	49	F	Het	Hm.Ob	+5.0	+4.0	+6.0	+6.0
225.	M	53	A	Het	Hm.	+1.5	+1.5	+1.5	+1.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
226.	M	13	F	bl	Hm.	+7.0	+3.5	+6.0	+3.5
227.	M	9	F	Het	My.Ob.	−5.0	−9.0	−6.0	−2.5
228.	F	6	F	BR	Hm.	+6.0	+5.0	+8.0	+6.0
229.	F	5	F	Het	Hm.	+8.0	+8.0	+8.0	+8.0
230.	M	11	F	Het	Hm.	+3.0	+3.0	+2.5	+2.5
231.	F	10	F	bl	My.	−1.0	−1.0	−1.0	−1.0
232.	M	5	A	Het	Hm.	+3.0	+3.0	+3.0	+3.0
233.	M	10	F	BR	Hm.	+6.0	+5.0	+4.5	+4.5
234.	F	18	F	bl	Hm.	+5.0	+5.0	+5.0	+5.0
235.	F	26	A	bl	My.Ob.	−5.0	−2.5	−2.5	−6.0
236.	F	13	A	bl	Hm.	+5.0	+4.5	+5.0	+4.5
237.	M	62	F	bl	Hm.	+1.5	+1.5	+1.5	+1.5
238.	M	68	F	Het	Hm.	+0.75	+0.75	+0.75	+0.75
239.	M	80	F	bl	Hm.	+2.5	+3.0	+3.0	+3.0
240.	M	42	F	Het	Hm.	+2.5	+2.0	+2.5	+2.0
241.	F	20	A	bl	My.	−1.25	−1.25	−1.25	−1.25
242.	M	67	F	Het	My.	−1.5	−3.5	−0.5	−1.5
243.	M	13	F	Het	My.	−3.0	−3.0	−3.0	−3.0
244.	M	12	F	bl	Hm.	+4.5	+2.0	+4.5	+2.0
245.	M	13	F	Het	Hm.	+3.5	+3.5	+6.0	+2.0
246.	M	13	F	bl	Hm.	+6.0	+6.0	+6.0	+6.0
247.	F	11	F	bl	My.Ob.	−0.5	−3.0	−1.25	−1.25
248.	M	9	F	bl	Hm.	+5.5	+5.5	+5.5	+5.5
249.	M	13	F	bl	Hm.	+7.0	+7.0	+7.0	+7.0
250.	M	11	A	Het	Hm.	+7.0	+7.0	+7.0	+7.0

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
251.	F	48	A	Het Hm.	+4.0	+2.5	+5.0	+3.0
252.	M	12	F	bl Hm.	+4.0	+3.0	+4.0	+3.0
253.	M	9	A	Het Hm.	+7.0	+7.0	+7.0	+7.0
254.	F	8	F	BR Hm.	+4.0	+4.0	+4.0	+4.0
255.	M	7	F	Het Hm.	+2.75	+2.75	+2.75	+2.75
256.	F	5	F	bl Hm.	+3.0	+3.0	+3.0	+3.0
257.	F	12	A	Het My.	−1.5	−1.5	−1.5	−1.5
258.	F	13	F	Het My.	−1.0	−1.0	−1.0	−1.0
259.	M	13	A	bl Hm.	+10.0	+6.0	+9.0	+8.0
260.	M	9	A	Het Hm.	+6.0	+3.5	+5.0	+3.0
261.	M	9	F	Het Hm.	+3.0	+3.0	+3.5	+3.5
262.	F	22	F	Het Hm.	+1.0	+0.75	+1.0	+0.75
263.	F	47	F	Het HmOb	+2.5	+1.0	+1.0	+2.5
264.	M	10	F	Het Hm.	+5.0	+5.0	+5.0	+5.0
265.	F	9	F	bl Hm.	+6.0	+3.0	+5.5	+5.0
266.	M	13	F	bl Hm.	+7.0	+6.0	+7.0	+7.0
267.	M	13	A	bl My.	−4.0	−4.5	−2.0	−4.0
268.	F	11	F	Het My.	−4.0	−7.5	−0.5	−2.5
269.	F	11	F	Het Hm.	+8.0	+3.5	+7.0	+3.5
270.	M	5	F	bl Hm.	+3.0	+3.0	+3.0	+3.0
271.	F	7	F	bl Hm.	+7.0	+4.0	+7.0	+4.0
272.	M	13	A	bl Hm.	+7.0	+6.0	+7.0	+6.0
273.	M	18	F	bl Hm.	+5.5	+4.0	+5.5	+4.0
274.	F	64	F	bl Hm.	+3.5	+0.75	+3.5	+0.75
275.	F	75	F	Het Hm.	+4.0	+4.0	+4.5	+4.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
276.	M	9	F	Het	Hm.	+1.25	+1.25	+1.25	+1.25
277.	M	45	F	bl	My.	−1.0	−1.25	−1.0	−1.5
278.	M	17	F	Het	Hm.	+1.25	+1.25	+1.25	+1.25
279.	F	7	A	BR	Hm.Ob.	+4.5	+3.5	+4.5	+4.5
280.	F	8	A	Het	Hm.	+8.0	+9.0	+8.0	+9.0
281.	F	5	F	Het	Hm.	+5.5	+4.5	+5.5	+4.5
282.	F	13	F	Het	My.	−1.75	−1.75	−1.5	−1.5
283.	F	7	F	bl	Hm.	+2.5	+2.5	+2.5	+2.5
284.	M	13	F	Het	Hm.	+9.0	+4.0	+8.0	+4.0
285.	M	10	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
286.	M	5	F	Het	Hm.	+3.5	+3.5	+3.5	+3.5
287.	M	65	A	Het	Hm.	+1.5	+2.25	+1.25	+1.25
288.	F	37	F	bl	My.	−2.5	−3.0	−2.5	−3.5
289.	M	66	F	Het	Hm.	+3.75	+3.75	+3.75	+3.75
290.	M	63	F	bl	Hm.	+1.0	+3.0	+0.5	+1.25
291.	F	27	F	Het	My.	−9.0	−9.0	−12.0	−12.0
292.	M	55	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
293.	F	53	A	Het	Hm.	+2.0	+2.0	+2.0	+2.0
294.	F	37	F	Het	Hm.	+5.0	+5.0	+6.0	+6.0
295.	F	31	F	Het	Hm.	+2.0	+2.0	+2.5	+2.5
296.	F	36	A	Het	Hm.	+2.5	+2.5	+2.5	+2.5
297.	F	48	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
298.	M	49	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
299.	F	24	F	bl	Hm.	+1.0	+1.0	+1.0	+1.0
300.	F	51	F	bl	Hm.	+1.0	+3.0	+1.0	+3.5

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
301.	F	5	A	Het	Hm.Ob.	+4.5	+7.0	+7.0	+4.5
302.	F	9	A	bl	Hm.	+1.5	+1.5	+1.5	+1.5
303.	F	5	F	BR	Hm.	+5.0	+5.0	+5.0	+5.0
304.	M	8	F	BR	Hm.Ob.	+6.0	+5.0	+4.5	+4.5
305.	F	9	F	bl	Hm.	+3.0	+3.0	+3.0	+3.0
306.	M	5	F	Het	Hm.	+5.0	+5.0	+5.0	+5.0
307.	F	9	F	Het	Hm.	+2.0	+2.0	+2.0	+2.0
308.	F	5	F	bl	Hm.	+3.5	+3.5	+4.5	+4.0
309.	F	30	A	Het	Hm.Ob.	+2.0	+5.0	+6.0	+3.5
310.	M	9	F	bl	Hm.	+5.0	+5.0	+5.0	+5.0
311.	F	38	F	Het	My.	−5.0	−9.0	−14.0	−14.0
312.	M	52	F	bl	Hm.	+1.25	+1.25	+1.25	+1.25
313.	F	44	A	Het	Hm.	+1.0	+1.0	+1.0	+1.0
314.	M	25	F	Het	Hm.	+8.0	+6.0	+8.0	+6.0
315.	F	64	F	Het	Hm.	+1.25	+1.25	+1.25	+1.25
316.	F	14	A	Het	Hm.Ob.	+4.0	+0.5	+0.75	+4.0
317.	M	9	F	BR	Hm.	+13.0	+10.0	+14.0	+10.0
318.	M	12	A	Het	Hm.	+6.0	+6.0	+6.0	+6.0
319.	F	8	F	Het	My.	−4.0	−9.0	−4.0	−9.0
320.	M	8	A	BR	Hm.	+5.0	+5.0	+5.0	+5.0
321.	M	8	A	Het	My.	+4.0	−0.5	+4.0	−1.0
322.	M	13	F	bl	Hm.	+2.5	+2.5	+3.5	+3.5
323.	F	72	R.A.	BR	Hm.	+1.0	+1.0	+1.0	+1.0
324.	F	64	F	Het	Hm.	+3.0	+3.0	+3.0	+3.0
325.	F	14	A	Het	My.	−1.5	−2.0	−1.0	−2.25

Case No.	Sex	Age	Ear	Iris		Right Hor.	Right Vert.	Left Hor.	Left Vert.
326.	F	15	F	Het	Hm.	+1.25	+1.25	+1.25	+1.25
327.	M	9	F	bl	Hm.	+1.25	+1.25	+1.25	+1.25
328.	M	7	F	bl	Hm.	+1.75	+1.75	+1.75	+1.75
329.	M	13	F	Het	My.Ob.	−1.5	−1.5	−1.5	+1.25
330.	M	7	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
331.	M	5	F	bl	Hm.Ob.	+5.0	+4.0	+4.0	+4.0
332.	F	5	F	Het	Hm.	+6.0	+6.0	+6.0	+6.0
333.	F	48	F	BR	Hm.	+1.5	+1.75	+1.5	+2.0
334.	F	40	F	bl	Hm.	+2.5	+2.5	+2.5	+2.0
335.	F	22	F	BR	My.	+2.5	−2.0	+3.5	−1.0
336.	F	17	F	Het	My.	−1.0	−1.0	−1.0	−1.0
337.	F	43	A	Het	Hm.	+1.25	+1.25	+2.5	+2.5
338.	F	28	A	Het	Hm.	+1.25	+1.25	+1.25	+1.25
339.	M	10	F	bl	Hm.	+2.5	+2.5	+2.5	+2.5
340.	M	14	A	Het	Hm.	+4.0	+4.0	+4.0	+4.0
341.	M	13	A	BR	My.	−1.0	−2.0	−1.0	−2.0
342.	F	8	F	Het	Hm.	+2.5	+2.5	+2.5	+2.5
343.	M	10	F	bl	Hm.	+1.5	+1.5	+2.75	+2.75
344.	M	7	A	bl	Hm.	+5.0	+5.0	+4.0	+4.0
345.	F	11	F	BR	Hm.Ob.	+3.5	+3.5	+4.0	+2.5
346.	F	7	A	bl	Hm.	+7.0	+7.0	+7.0	+3.5
347.	M	10	F	bl	Hm.	+2.5	+2.5	+2.5	+2.5
348.	M	6	F	Het	Hm.	+1.5	+1.5	+1.5	+1.5
349.	F	28	A	Het	Hm.	+1.25	+1.25	+1.25	+1.25
350.	M	47	F	bl	Hm.	+1.25	+1.25	+1.25	+1.25

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
351.	M	38	A	bl Hm.	+1.75	+1.75	+1.75	+1.75
352.	F	32	A	bl My.	+2.5	-1.5	+2.25	-2.25
353.	F	20	A	bl Hm.	+1.75	+1.75	+1.75	+1.75
354.	F	28	F	Het My.	-1.0	-1.5	-1.5	-2.0
355.	F	69	F	Het Hm.	+6.0	+5.0	+5.0	+5.0
356.	F	16	F	bl My.	+2.0	-0.5	+4.0	-1.5
357.	F	32	A	Het My.	-2.25	-1.5	-2.25	-1.75
358.	M	17	F	Het Hm.	+0.75	+0.75	+0.75	+0.75
359.	M	13	F	bl Hm.	+6.0	+6.0	+6.0	+6.0
360.	M	14	F	bl Hm.	+3.0	+3.0	+3.0	+3.0
361.	M	16	A	bl My.	+3.5	-0.5	-0.5	-0.5
362.	F	7	F	bl My.	-6.0	-6.0	-6.0	-6.0
363.	M	13	F	bl Hm.Ob.	+8.0	+5.0	+5.0	+8.0
364.	M	6	F	bl Hm.	+8.0	+8.0	+8.0	+8.0
365.	F	13	A	bl Hm.	+6.0	+2.5	+5.0	+0.5
366.	M	13	F	bl My.	-1.5	-1.5	-1.5	-1.5
367.	M	13	F	Het My.	-2.0	-2.0	-1.0	-1.0
368.	F	52	F	Het Hm.	+8.0	+4.0	+8.0	+4.0
369.	F	19	F	bl Hm.	+1.0	+1.0	+1.0	+1.0
370.	M	45	F	BR Hm.	+2.0	+2.0	+2.0	+2.0
371.	M	57	F	Het Hm.	+3.0	+3.0	+3.0	+3.0
372.	M	47	F	bl Hm.	+2.5	+0.5	+2.5	+0.5
373.	M	10	A	bl My.	-1.25	-1.25	-1.25	-1.25
374.	M	11	F	bl Hm.	+2.25	+2.25	+2.25	+2.25
375.	F	10	A	Het Hm.	+5.0	+5.0	+5.0	+5.0

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
376.	F	6	F	bl Hm.	+3.5	+3.5	+3.0	+3.0
377.	F	10	F	bl Hm.	+4.0	+4.0	+4.0	+4.0
378.	M	9	F	Het Hm.	+4.0	+4.0	+4.0	+4.0
379.	M	9	F	Het Hm.	+4.0	+4.0	+7.0	+7.0
380.	M	24	F	bl My.	−2.5	−2.5	−2.5	−2.5
381.	F	6	F	bl Hm.	+4.5	+4.5	+4.5	+4.5
382.	F	17	F	Het My.	−5.0	−5.0	−1.5	−2.5
383.	F	16	A	Het Hm.	+0.75	+0.75	+0.75	+0.75
384.	M	6	F	Het Hm.	+8.0	+8.0	+5.5	+5.5
385.	M	15	F	bl Hm.Ob.	+8.0	+4.0	+8.0	+4.0
386.	F	11	A	Het Hm	+3.0	+3.0	+3.0	+3.0
387.	M	13	F	Het Hm.	+8.0	+6.0	+8.0	+6.0
388.	F	11	F	bl Hm.	+0.5	+0.5	+0.5	+0.5
389.	M	11	F	bl Hm.Ob.	+7.0	+5.0	+5.0	+7.0
390.	F	70	F	Het Hm.	+2.5	+3.0	+3.0	+3.0
391.	F	4	F	Het Hm.	+3.0	+3.0	+3.0	+3.0
392.	M	8	F	Het Hm.	+3.0	+3.0	+3.0	+3.0
393.	F	24	F	Het My.	−8.0	−8.0	−8.0	−8.0
394.	M	60	F	bl Hm.Ob.	+2.0	+5.0	+6.0	+2.0
395.	F	56	F	Het Hm.	+1.0	+1.0	+1.0	+1.0
396.	M	2	F	bl Hm.	+3.0	+3.0	+3.0	+3.0
397.	M	8	F	Het Hm.	+7.0	+7.0	+9.0	+9.0
398.	F	16	F	bl Hm.	+1.0	+1.0	+1.0	+1.0
399.	F	18	F	Het My.	−1.5	−1.5	−1.5	−2.0
400.	F	44	F	Het Hm.	+7.0	+7.0	+7.0	+7.0

Case No.	Sex	Age	Ear	Iris	Right		Left	
					Hor.	Vert.	Hor.	Vert.
401.	F	61	F	bl Hm.	+3.5	+3.5	+3.5	+3.5
402.	M	12	F	bl Hm.	+2.0	+1.0	+4.0	+1.0
403.	M	13	A	Het Hm.	+6.0	+6.0	+6.0	+6.0
404.	M	14	A	Het Hm.	+5.0	+5.0	+5.0	+5.0
405.	M	15	F	bl Hm.	+4.0	+4.0	+5.0	+5.0
406.	F	10	F	bl Hm.	+8.0	+6.0	+8.0	+6.0
407.	M	15	A	bl My.	-3.5	-3.5	-3.0	-3.0
408.	M	11	F	Het Hm.	+6.0	+6.0	+6.0	+6.0
409.	M	8	F	BR Hm.	+5.0	+5.0	+5.0	+5.0
410.	M	12	A	bl Hm.	+4.0	+0.5	+5.0	+3.0
411.	M	14	F	bl My.	-5.0	-5.0	-5.0	-5.0
412.	F	42	A	Het My.	-1.5	-2.0	+0.75	+0.75
413.	F	92	F	bl Hm.	+1.5	+1.5	+1.5	+1.5
414.	M	47	F	Het Hm.Ob.	+0.5	+5.0	+5.0	+2.0
415.	M	24	A	bl Hm.Ob.	+7.0	+2.0	+2.0	+5.0
416.	M	74	F	Het My.	-12.0	-12.0	-12.0	-12.0
417.	M	58	A	Het Hm.	+0.5	+1.0	+0.5	+1.0
418.	M	55	F	Het Hm.	+3.0	+3.0	+3.0	+3.0
419.	M	65	F	bl Hm.	+6.0	+6.0	+7.0	+7.0
420.	F	67	F	Het Hm.	+2.25	+2.25	+2.25	+2.25
421.	M	60	A	Het Hm.	+3.0	+3.0	+3.0	+3.0
422.	M	45	F	bl Hm.	+1.5	+1.5	+1.5	+1.5
423.	M	70	F	Het Hm.	+2.5	+2.5	+3.0	+2.0
424.	F	65	F	Het Hm.	+1.5	+1.0	+1.5	+1.0
425.	M	59	F	bl Hm.Ob.	+6.0	+6.0	+8.0	+11.0

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
426.	M	11	F	Het Hm.	+1.75	+1.75	+1.75	+1.75
427.	M	10	F	Het Hm.	+4.0	+4.0	+6.0	+6.0
428.	M	6	F	Het Hm.	+6.0	+6.0	+7.0	+6.0
429.	F	5	F	bl Hm.	+4.0	+4.0	+4.0	+4.0
430.	F	5	F	BR Hm.	+4.5	+3.5	+3.0	+3.0
431.	F	13	F	bl My.	−1.75	−1.75	−1.75	−1.75
432.	F	5	F	Het Hm.	+6.0	+4.5	+4.5	+3.0
433.	F	10	F	bl Hm.	+1.75	+1.75	+1.75	+1.75
434.	F	10	A	bl Hm.	+9.0	+7.0	+9.0	+7.0
435.	M	7	F	BR Hm.	+2.5	+2.5	+2.5	+2.5
436.	F	25	A	bl My.	−1.0	−1.0	+1.0	+1.0
437.	M	43	A	Het My.	+1.5	+1.0	−0.5	−0.5
438.	F	22	F	bl My.	−9.0	−14.0	−10.0	−14.0
439.	M	6	F	bl Hm.	+6.0	+6.0	+6.0	+6.0
440.	M	14	A	Het Hm.	+5.0	+5.0	+5.0	+5.0
441.	M	14	F	bl Hm.	+11.0	+11.0	+11.0	+11.0
442.	F	9	F	Het My.	−8.0	−8.0	−7.0	−8.0
443.	F	14	A	Het My.	−2.0	−2.5	−0.5	−0.5
444.	F	5	F	bl Hm.	+8.0	+7.0	+8.0	+7.0
445.	F	13	F	Het Hm.	+6.0	+6.0	+6.0	+6.0
446.	M	15	F	Het My.	−1.5	−0.75	−4.0	−4.0
447.	F	12	A	bl Hm.	+7.0	+7.0	+7.0	+7.0
448.	M	61	F	Het Hm.	+3.0	+3.0	+2.5	+0.25
449.	F	69	F	Het Hm.	+2.25	+2.0	+2.25	+2.0
450.	M	59	F	bl Hm.Ob.	+6.0	+6.0	+8.0	+11.0

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
451.	F	33	F	bl Hm.	+6.0	+2.0	+5.0	+2.0
452.	M	55	F	bl Hm.	+3.5	+3.5	+3.5	+3.5
453.	M	18	A	bl Hm.	+2.0	+2.0	+2.0	+2.0
454.	M	50	F	bl Hm.	+1.0	+1.0	+1.0	+1.0
455.	M	30	F	Het Hm.Ob.	+10.0	+7.0	+7.0	+10.0
456.	M	62	F	Het Hm.	+2.0	+2.0	+2.0	+2.0
457.	M	62	F	Het Hm.	+1.5	+1.5	+1.5	+1.5
458.	M	41	F	bl Hm.	+2.0	+2.0	+2.0	+2.0
459.	F	9	F	BR Hm.	+10.0	+10.0	+10.0	+10.0
460.	F	11	F	bl Hm.	+4.5	+3.5	+4.5	+3.5
461.	M	9	F	Het Hm.	+1.5	+1.5	+1.5	+0.5
462.	M	12	F	bl Hm.	+9.0	+9.0	+9.0	+9.0
463.	M	10	F	Het Hm.	+4.0	+2.0	+4.0	+2.0
464.	F	32	A	Het Hm.	+1.25	+1.0	+1.5	+1.0
465.	F	51	F	Het Hm.	+1.75	+1.75	+1.75	+1.75
466.	F	60	A	Het Hm.	+1.75	+1.75	+1.75	+1.75
467.	M	70	F	bl My.	−5.0	−5.0	−5.0	−5.0
468.	F	38	F	bl Hm.	+1.0	+1.0	+1.0	+1.0
469.	M	16	A	Het Hm.	+1.0	+1.0	+1.0	+1.0
470.	F	6	F	Het My.	−4.0	−4.0	−4.0	−4.0
471.	M	31	F	Het Hm.	+1.0	+1.0	+1.25	+1.25
472.	M	70	F	Het My.	−3.0	−3.0	−3.0	−3.0
473.	F	13	F	bl My.	−5.0	−9.0	−5.0	−9.0
474.	M	11	F	bl Hm.	+3.0	+3.0	+5.5	+5.5
475.	F	8	F	Het Hm.	+2.5	+2.5	+2.5	+2.5

Case No.	Sex	Age	Ear	Iris	Right Hor.	Right Vert.	Left Hor.	Left Vert.
476.	F	5	A	bl Hm.	+6.0	+6.0	+5.0	+5.0
477.	F	10	F	bl Hm.Ob.	+4.5	+1.25	+3.5	+3.5
478.	M	7	F	Het Hm.	+7.0	+7.0	+8.0	+8.0
479.	F	12	A	Het Hm.	+8.0	+3.5	+9.0	+4.0
480.	M	8	F	Het Hm.	+6.0	+6.5	+7.0	+6.0
481.	F	7	F	bl Hm.	+3.5	+3.5	+3.5	+3.5
482.	M	8	F	BR Hm.	+1.5	+1.5	+1.5	+1.5
483.	M	65	F	bl Hm.	+1.0	+1.0	+1.0	+1.0
484.	M	29	F	Het Hm.	+5.0	+5.0	+5.0	+5.0
485.	F	39	F	BR Hm.	+2.0	+2.0	+2.0	+2.0
486.	F	21	F	Het My.	−3.0	−3.0	−3.0	−3.0
487.	F	50	F	Het Hm.	+1.75	+1.75	+1.75	+1.75
488.	M	30	F	bl Hm.	+1.25	+1.25	+1.25	+1.25
489.	M	78	F	bl Hm.	+2.25	+2.25	+2.0	+2.0
490.	M	13	A	bl Hm.	+1.25	+1.25	+1.25	+1.25
491.	F	52	F	Het Hm.	+0.5	+0.5	+0.75	+0.75
492.	F	55	F	Het Hm.	+1.5	+1.5	+1.5	+1.5
493.	M	14	F	Het Hm.	+5.0	+2.0	+4.0	+4.0
494.	M	10	F	BR Hm.	+5.0	+5.0	+5.0	+5.0
495.	M	8	F	Het Hm.	+4.5	+3.5	+3.5	+3.5
496.	F	9	F	bl Hm.	+2.0	+2.0	+2.0	+2.0
497.	F	7	F	Het My.	+1.5	−3.5	+1.5	−2.0
498.	M	13	F	Het Hm.	+8.0	+8.0	+7.0	+7.0
499.	M	13	F	bl My.	−9.0	−9.0	−8.0	−8.0
500.	M	13	F	bl Hm.	+7.0	+7.0	+7.0	+7.0

Literature.

In the following list papers known to me only by quotation are indicated by stating the origin of the reference. As the thesis is based upon observed pedigrees no attempt has been made to provide an exhaustive bibliography.

Special acknowledgement must be made by all ophthalmologists who write upon the subject of heredity in eye conditions to the authors of the three works listed below.

The Treasury of Human Inheritance, edited by Karl Pearson, Volume II. Nettleship Memorial Volume by Dr. Julia Bell.

Kurzes Handbuch der Ophthalmologie, edited by F. Schieck and A. Brückner, Volume I, section on the Heredity of the Eye by A. Franceschetti.

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