SEX LINKAGE IN MAN[1]

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INTRODUCTION

The fact that chromosomes play an extraordinarily important part in determining development is now established. Not only chromosomes, as a whole, thus function, but also their constituent genes play a specific rôle. And each such gene plays a rôle that, on the one hand, is general in the development of the organism and, on the other hand, specific for a particular morphological or chemical quality of the organism.

Each gene, we must believe, is, ordinarily, located in a particular chromosome. One of these chromosomes is found in most of the higher organisms to be to a large degree determinative of sex. It is, accordingly, called the

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sex-chromosome. A number of genes are located in the sex-chromosome and they are linked with sex itself in an interesting and curious way. In humans the female somatic cells have two sex-chromosomes (XX), one from each parental germ cell, while the male has only one X-chromosome and this is derived from the egg. It is associated with the Y-chromosome which carries few active genes.

A consequence of these relations is that sperm cells that carry an affected X-chromosome become progenitors of daughters half of whose eggs, in turn, carry the affected X-chromosome. If such eggs produce males, the males will be affected; if females, their defective X-chromosome will be balanced by a normal X-chromosome from the sperm and the females will either not show somatically or phaenotypically the defect that they carry, or will show it in a low grade of expression (see figure 1).

Now all of the sex-linked traits are linked, not with sex alone but also with each other. Accordingly we expect to find sex-linked traits associated with each other in inheritance.

It was this consideration that led the Research Committee of the AMERICAN MEDICAL ASSOCIATION to start a study of some human families with haemophilia to learn if color-blindness, or any other sex-linked trait, was in them linked with the haemophilia. Before giving our results (which were not as conclusive as hoped for) it may be well to review our knowledge of the best studied sex-linked traits in man. These are: color-blindness, haemophilia, optic nerve atrophy; also, but less extensively studied, night blindness, some cases at least of muscular atrophy, hypoplasia of white brain substance (Pelizaeus-Merzbacher disease), and some strains of myopia and of multiple sclerosis. Still other sex-linked traits have been cited, but the evidence for them is still very limited.

It is proposed to consider the best known of these sex-linked traits.

COLOR-BLINDNESS

It has been known for over a century and a quarter that some persons are defective in the color sense. Three main types of color defect are known.

(a) Achromatic vision. The central region (fovea) is alone sensitive to light. The loss of function is probably due to defective development of the cones. This condition is not known to have any hereditary factor.

(b) Red-green color-blindness; dichromatic vision. This includes the red-blind and the green-blind. Violet-blind persons have been described, but the condition is very rare. The commonest sub-type is red-blindness, called protanopia or blindness to the first essential (red) constituent of the

spectrum. Persons thus affected see the red end as an extremely low, unintense yellow. The green band also appears yellow and bright. The other sub-type includes green-blindness, called deuteronopia, or blindness to the second essential (green) constituent of the spectrum. Persons thus affected see the red end as a yellow that is only slightly reduced in intensity from normal yellow, while the green band is a yellow that is much less bright than in the case of the red-blind.

(c) Includes anomalous trichromatic vision. Persons of this type see the red, yellow and green of the spectrum; but red and green mixed in the proportions that give yellow to the normal eye do not give a good yellow to them. Two sub-groups can be distinguished here also.

Persons of one sub-group say that the mixed color is green; to make yellow more red of the spectrum must be added—this makes a yellow that is rather dull. Such persons are called "green-see-ers" or protanomals.

Persons of the other sub-group say the mixture of green and red that ordinarily gives yellow appears to them red. More green has to be added; then they see a bright yellow. They are called "red-see-ers" or deuteranomals.

The genetic problem is the relationship of these five conditions, normals, protanomals and protanops, on the one hand, and deuteranomals and deuteranops, on the other.

Before entering more deeply into the problem it is necessary to consider the statistics of color-blindness in the general population. It is commonly said that, in Europe generally, there are 4 percent of men and 0.4 percent of women affected; that is, one tenth as many women as men.

DANFORTH (1924) has argued that there is something incompatible with these proportions and the probability that the proportions of color-blind in the population are not changing. It may be said, parenthetically, that since color-blindness has been measured in large numbers of children only during the present generation we really have no basis for the conclusion that the proportion is not changing.

On the hypothesis that red-green color-blindness is due to a mutation in a gene of the sex chromosome (the X-chromosome) then the following considerations will hold. Since there is only one X-chromosome in the male, there is the same proportion of affected X-chromosomes in the male population as there is of color-blind males, namely 4 percent. Also it may be said that, for the same reason, 4 percent of the X-bearing male sperm of the entire population are defective in the gene for color discrimination that is carried in the X-chromosome. The proportion of normal to defective color genes in the male X germ-plasm is, therefore, as 96:4.

Since male zygotes derive their X-chromosomes exclusively from the egg, then in the whole population the proportion of eggs containing a defective X-chromosome is 4 percent; 96 percent have an unaffected X-chromosome.

In female zygotes there are 3 possible combinations (since each female zygote has 2 X-chromosomes). Since in all X-bearing sperm cells we have the ratio 96 percent X:4 percent X′ and in all eggs 96 percent X:4 percent X′ (where X′ refers to the X-chromosome carrying the affected gene) then in all zygotes we shall have normals 0.96×0.96 or 0.9216. Of conductors 2 times 0.96×0.04 or 0.0768. Of color blind 0.04×0.04 or 0.0016.

The above computation gives us 0.16 percent color-blind females in the population instead of the 0.4 percent alleged to occur. We see, thus, that a population consisting of 4 percent color-blind men and 0.4 percent color-blind women will produce only 0.16 percent color-blind women in the next generation, while the proportion of affected men remains at 4 percent. Thus the proportion of color-blind women to color-blind men will tend rapidly to diminish in successive generations; but if it does, the proportion of color-blind men will also diminish.

SCHIÖTZ (1922) by means of refined methods of testing for color-blindness, reaches a conclusion that 10 percent of males and 1 percent of females are color-blind. Such a pair of ratios can maintain themselves approximately in successive generations. Doubt has been cast, however, upon the reliability of SCHIÖTZ's determinations.

WAALER (1927) has examined 9000 children in the schools of Oslo using the Ishihara test as a routine test and examining by means of the Nagel anomaloscope all whose reactions to the Ishihara tests were not normal. He also examined the entire family, as far as possible, of all of the boys and the girls who had defective color discrimination.

All males proved themselves to be either normal or to belong to one of the four aberrant types: protanomal, protanops, deuteranomal, deuteranops; and, in transmission, there proceeds from each male a chromosome of a type corresponding to the condition that the male shows somatically.

The females, however, do not show somatically or phaenotypically the whole content of abnormality in the X-chromosome since they have two such chromosomes and these may be either similar or unlike. The composition of the X-chromosomes of the mother is demonstrated by the color discrimination of her sons. Also the color discrimination of her father and brothers will help with the analysis, since she receives one of her X-chromosomes from her father and one from her mother, whose constitution is in part indicated by the condition of her brother. As a result of this colossal investigation of WAALER'S it appears that the protanomal condition is

dominant over the protanops; the deuteranomal is dominant over the deuteranops; while the normal condition dominates over all. The normal, the protanomal and the protanops constitute three members in an allelomorphic series. The gene for each is located in the same point of the chromosome. Similarly, normal, deuteranomal, and deuteranops constitute an allelomorphic series located in the same gene. The author is inclined to conclude that the genes for all five conditions are identical but suffer varying amounts of kinds of damage.

WAALER'S statistics indicate that 8 percent of the population of boys examined show some type of abnormality in color discrimination. One would expect 0.64 percent of the girls to show color-blindness. There are actually found 0.44 percent $\pm$ 0.07. The deviation from expectation, while considerable, is not too improbable in view of the considerable size of the probable error. The statistical findings of WAALER, therefore, show a relation between abnormal males and females that can persist in successive generations.

Anatomical basis of red-green color-blindness

A thorough critical examination of the literature, with a study of some new families, has been recently made by BELL (1926). She points out that it is uncertain upon just what modifications of the normal color discriminating apparatus color-blindness depends. Indeed, the basis of normal color discrimination is not certainly known. There is some evidence that the cones of the retina are part of the color discriminating apparatus. Thus LARSEN (1921) found that in totally color-blind persons, whose eyes he sectioned, the cones of the fovea "were short and plump where they are normally found to be long and slender." Also they had either very short outer members or these were wholly absent. There is some evidence that a central-cerebral defect is also involved, since "disturbances of cerebral origin from pathological processes may cause total color-blindness without any affection of the retinal structures." (BELL 1926, p. 172).

Inheritance of red-green color-blindness

Color-blindness is commonly considered to be due to a recessive gene mutation located in the sex chromosome.

If the father is color-blind, his sole X-chromosome carries the defective gene. If the mother is color-blind, both of the two X-chromosomes, by hypothesis, carry the defective gene. But a mother may carry the defective gene in one of her X-chromosomes, while the other is unaffected. Such a mother, called a conductor, will be phaenotypically normal.

While all the eggs carry an X-chromosome, only half of the sperm cells do (the other half carrying the Y-chromosome which plays a small rôle in inheritance). The sons get their single X-chromosome from the egg only; so if the mother is without gametic defect none of the sons will be color-blind even if the father is. The daughters get an X-chromosome each from the egg and sperm. If the X-chromosomes of the egg are all without the gene defect, then the daughters can distinguish colors even if the sperm cell brings in a gene-defect in its X-chromosome. In the latter case, the heterozygous daughter can pass on the defective X-chromosome to half of her offspring. In the case of the sons half will be color-blind; in the case of the daughters half will be conductors—forming some eggs containing the defective X-chromosome.

Do the heterozygous females always have normal color discrimination? BELL (1896, p. 195) cites one sibship containing three color-blind females, the father of whom has been definitely tested by NETTLESHIP (1912) and pronounced to have normal color vision; and in several unquestionable cases color-blind women have been demonstrated to have some sons with normal color vision. In BELL'S (1926, p. 233) pedigree (chart 418, II 4), a woman, aged 54, was thoroughly tested by wools, Nagel's cards and the Stilling test and found to be definitely color-blind; she required the help of others in choosing her dresses. She had a number of daughters and 7 sons. Three of these sons are clearly color-blind. Of the 4 others 3 were tested for color-blindness. The first was tested by Sir J. H. PARSONS, who found him normal with Holmgren's wools, Stilling test and colored lights. The other 2 boys were given an equally rigid test and showed fine color discrimination. Of the 4 daughters tested all were found normal. The condition of color vision of the parents of the affected mother is not definitely known. On the chromosome theory of heredity, it seems most probable that (unless the father was color-blind) the mother was heterozygous for color discrimination, and that the normal gene is imperfectly dominant. Thus we conclude that heterozygous females sometimes lack perfect color discrimination.

In figure 440 of BELL'S work (1926, p. 238) the "mother" (VI 13) is color-blind and has a color-blind father and a carrier mother; and at least 2 of her 3 sons are color-blind. Except that *all* sons should be color-blind, this accords with expectation, since in the "mother" both X-chromosomes are probably affected.

A summary of cases given by BELL is instructive. When both parents are color-blind all (4) sons and (5) daughters are color-blind. When the father is affected and the mother's stock is so likewise, 49 percent of sons

and 37 percent of daughters are affected. When both parents are normal and the mother's stock is affected 61 percent of the sons and 2 percent of the daughters are affected. Even when the mother is affected and the father normal only 3 percent of the daughters are affected. There is no doubt that color-blind fathers have carrier daughters who, in turn, have color-blind sons. That is, the defective chromosome passing through the (heterozygous) daughter is transmitted to half of her sons, who thus lack capacity for color discrimination.

HAEMOPHILIA

Normally the blood flows in well circumscribed, walled spaces in the body—the blood vessels; if the walls of the vessels are cut blood has the property of making a temporary wall, or plug, by clotting.

The irregularities in the physical behavior of blood are due (1) to weaknesses, or abnormalities, of the vessel walls, permitting extravasation into the tissues; (2) to abnormalities of the clotting process or (3) to a combination of the two preceding.

The first and third classes of cases are recognized by the symptom of purplish spots arising in the skin in consequence of such extraversation of blood. The commonest types are known as purpuras, or purple spot diseases.

Of the purpuras, the first type is characterized by the tendency to form purple specks which flow together to form larger patches—usually on the legs and arms and often symmetrically. In extreme cases violent intestinal and gastric symptoms—pain and vomiting—occur. The patient usually recovers in a few days. The symptoms are accounted for on the ground that bodily toxins cause paralysis of capillaries, or larger vessels; so that tone and resistance to pressure are lost. Probably the loss of tone is due to a preceding intoxication of the spinal innervation of these finer blood-vessels. There is no evidence of an hereditary tendency.

In the other type of purpura and in the so-called haemophilia, there is an abnormality in the blood which interferes with normal clotting, so that the clotting or coagulation time is greatly delayed or clotting wholly inhibited. (*For the determination of coagulation-time.* There are several methods in use, such as those of VIERORDT, W. SCHULTZ, BÜRKER, MORAWITZ and BIERICH, WÖHLISCH, SAHLI-TONIO, KOLLMANN and others. The salt-plasm method of WOOLRIDGE and NOLF is highly spoken of by BAAR and STRANSKY (1928). It is applied as follows: The blood flowing from the vein of the arm is received into an equal quantity of 10 percent NaCl solution (2 marks on the test tube) and smartly centrifuged. There results

a salt-plasma that does not spontaneously coagulate. To test coagulation, 1 cc of this salt-plasma is diluted with 4 cc of distilled water in a test tube that has been well cleaned with alcohol and ether and dried. One drop of egg yolk is added. Every 5 minutes one observes whether or not the plasma is coagulated, by gentle inclination of the test tube. It is desirable always to make 2 parallel determinations and 2 controls with normal blood. Normal salt-plasma coagulates within half an hour; haemophilic blood often remains uncoagulated or shows after many hours to some days an often incomplete coagulation.)

Clotting is due to the formation of threads of fibrin in the blood plasma which entangle the corpuscles and form a plug. This is an invaluable property in preventing bleeding to death at wounds; but it is a dangerous property if it occurs inside of blood vessels, since the plug might well enter into and close up essential vessels, causing perhaps instant death. Fibrin is formed, however, only in the air; and by an interaction between a substance in the blood plasma and a substance in some of the cellular elements of the blood, particularly the blood platelets, which rapidly disintegrate in the presence of air. The substance in the plasma is called fibrinogen and the enzyme from the cells is called thrombin. It is the interaction of the two that produces fibrin.

Just as fibrin is formed only out of the blood plasma in the air, so thrombin is formed in the cells, but only in the presence of calcium. The calcium is necessary to the activation of the thrombin. Blood collected in a vessel containing a weak solution (a little over 0.1 percent) sodium oxalate will not clot; but if a saturated solution of sodium chloride be added it clots at once. It is believed that the calcium is necessary to the formation of the thrombin out of something in the cell—and this something HOWELL calls prothrombin or "thrombinogen." It is also called, by BORDET, (1920) zytozym.

It is HOWELL'S (1913) hypothesis that the prothrombin of the blood is ordinarily prevented from forming thrombin by a substance that he calls anti-thrombin. But in the air, cellular elements, or the plates in the blood, neutralize the action of the anti-thrombin and, in the presence of calcium, enable the prothrombin to form thrombin.

In the second type of purpura, sometimes called purpura haemorrhagica, or thrombopenic purpura, there occur spontaneous bleedings in skin (forming purple patches); at mucous membranes—nose, gums, etc.; and internal organs—such as kidney and retina. Usually there is no bleeding at joints as in haemophilia. An histological study of such blood indicates that the number of blood plates is much reduced—so that

thrombin can not be formed in normal amount. It is on this account that this disease is sometimes called thrombopenic purpura.

An hereditary history for this disease has been given in a number of cases, which indicate perhaps a dominant heredity. Possibly in one or more of the genes of an autosome there is a positive something that prevents the formation of blood plates in normal amount and thrombin-forming function.

In *haemophilia* the symptoms are:

(1) After a cut, a persistent hemorrhage occurs that is scarcely controllable by artificial means. From the smallest wound the blood may trickle for days and weeks.

(2) Spontaneous hemorrhages appear, especially, persistent nose bleed; also striking effusions into the joints, which become enlarged and blackened—"blood joints," or "bleeder joints."

Probably only males are affected and most affected males (60 percent) die before the age of 8 years. In the 11 percent that attain the age of 22 years, the symptoms are ameliorated and after about 40 they are never severe.

The degree of symptoms is variable and in respect to symptoms biotypes appear in various families.

Cause of haemophilia

BAAR and STRANSKY (1928) after examining the results of all experimental work on the subject conclude:

Neither the fibrogen content of the haemophilic blood, nor the thrombin content of the haemophilic serum is diminished. No increase of coagulation-inhibiting factors is found.

The disturbance of coagulation in haemophilia is thus to be sought in the first phase of thrombin formation.

Although there are divergent experimental results, BAAR postulates as most probable, an insufficiency of a cell enzyme (prothrombin of HOWELL or zytozym of BORDET) and its retarded relinquishment by the blood plates.

From this point of view there is a gene in the X-chromosome that determines the production of a normal amount (and kind) of zytozym (prothrombin) in the cells and especially cellular elements of the blood. In haemophilia this gene is modified—and in different degrees—resulting in biotypes of haemophilia of varying degrees of defect.

Two rules of inheritance have been suggested.

NASSE'S rule: Only males are affected; the disease is transmitted through unaffected daughters to their sons.

LOSSEN'S rule. No affected male has direct male descendants who are affected. The transmission is only from female to female or female to male; never from a male to his daughters.

It should be easy, one would think, to decide between the rules of NASSE and LOSSEN by examination of the pedigree charts that have been published. But such examination leads to much disappointment. Of the 235 pedigree charts published in the work of BULLOCK and FILDES (1911) the only ones that show grandchildren of a certainly affected male are: Nos. 373 (TENNA family), 382, 387, 389, 402, 408, 424, 426, 431, 436, 445, 462, 465, 468, 474, (478), 490, 493 bis, 512, 528, 535, 540, 541, 548, 562, 570, 581, 584. But No. (478) is regarded as a valueless pedigree by BULLOCK and FILDES. In the 27 significant pedigrees there are 31 affected males who have grandchildren. Together these 31 males have 47 daughters that have children. Together these daughters have 128 sons, and of these $78 \pm$ are affected. Thus there are $78 \pm$ haemophilic grandsons of affected males descended in the female line from affected grandfathers. Certainly this result is opposed to LOSSEN'S rule: "Nur Männer sind Bluter, vererben aber, wenn sie Frauen aus gesunden Familie heiraten, die Bluteranlage nicht." Of the 31 affected male progenitors of grandchildren there were only 3 who did not have affected grandsons. It is quite impossible to believe that of these 31 men 28 (or 90 percent) married wives belonging to haemophilic families. On the other hand there are some statistical irregularities in the pedigrees. Expectation is that one-half of the sons of "conductor" mothers will be haemophilics. Of 128 sons recorded, $78 \pm$ (some uncertainties) are regarded as bleeders. This is 14 more than expectation. Also, of these "conductor" mothers the daughters who have any haemophilic sons should have them in the proportion of 50 percent of all sons. Actually of 45 recorded 34 are given as bleeders. These deviations from expectation are too great to be due merely to insufficient numbers. It seems probable that a larger proportion of haemophilic sons than of normal sons is recorded. The recorder of the pedigrees has his attention focussed on bleeders in the family, he records all such; but he is less careful to inquire into and record non-bleeders.

It seems the most probable conclusion that haemophilia follows the usual course of sex-linked inheritance, which is stated in NASSE'S rule.

An important inquiry is: Where are the haemophilic females? Such are to be expected from certain matings, just as color-blind females arise from certain matings. Although bleeding females have been described, careful

analysis usually shows that they are either women affected with purpura or else they are very incomplete cases of true bleeding appearing in "con-

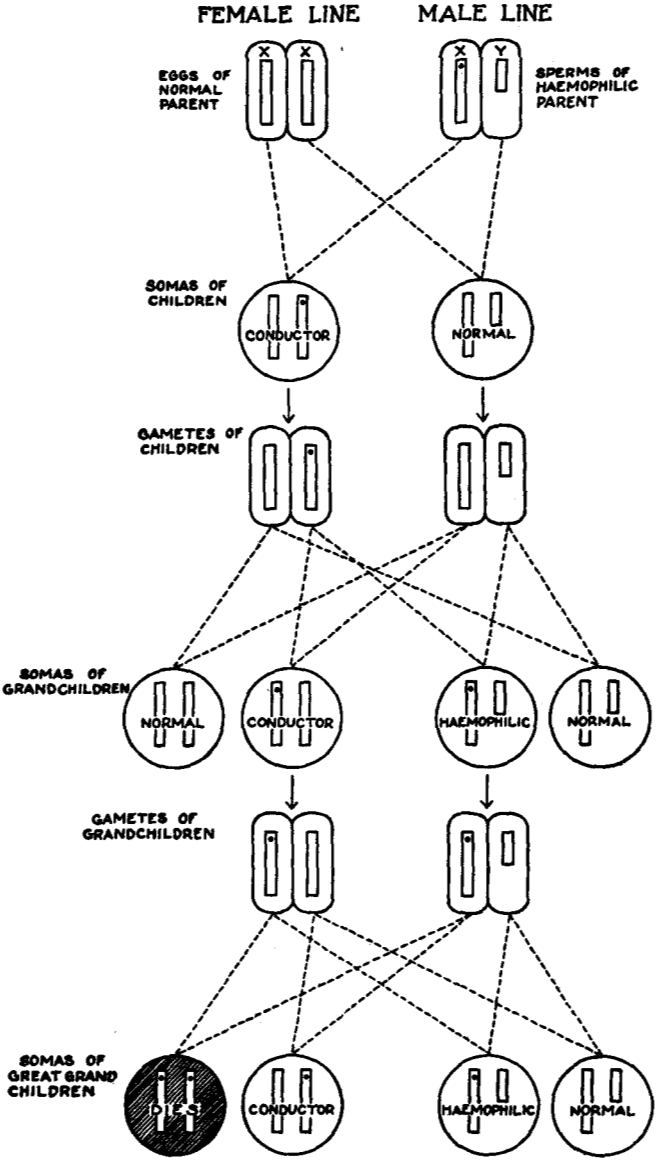

FIGURE 1.—Scheme of inheritance along male and female lines of the gene for haemophilia. Drawing by Miss M. B. CHAMBERS.

ductors" (that is heterozygous females). The most reasonable explanation of the absence of typical haemophilic symptoms in the female is that the

zygote that receives 2 affected X-chromosomes dies early, usually before birth (figure 1).

Hereditary Optic Nerve Atrophy (Leber's disease)

This disease commonly begins at adolescence with a loss of clear vision, due to the development of an area of partial, or total, blindness (scotoma) in the axis of vision. Just because this area is that of greatest color discrimination, color vision is greatly reduced. On ophthalmoscopic examination the disk of the optic nerve is found to be grayish or whitish instead of pink. In later stages the margins of the disk become ill defined; also the blood vessels of the retina become narrowed and more tortuous.

Hereditary opticus atrophy belongs to a genus of diseases that is characterized by degeneration of the optic nerve. In the genus are also (1) intoxication nerve atrophy, also called "neuritis axialis chronica sive actua," and (2) diabetic nerve atrophy.

Intoxication nerve atrophy appears subsequent to excessive use of alcohol or tobacco. Wood alcohol blindness belongs in this category. After abstinence vision is improved. In the hereditary form no improvement follows abstinence (though abuse of narcotics often precedes its onset). Also the narcotic type is often one-sided, while the hereditary type is bilateral—though vision may be affected in one eye earlier than the other. Moreover in the narcotic form the sexes are nearly equally affected; while in the hereditary type females are not usually affected. Also in the narcotic type onset is ordinarily slower and occurs later in life, and vision is less often completely impaired.

The diabetic species of optic nerve atrophy is associated with a high percentage of blood sugar and affects the sexes equally.

The specific diagnosis of hereditary opticus atrophy is based on the inability to control it by abstinence from narcotics, or on its non-association with high blood sugar, on a relatively early and sudden onset (usually under 28 or even 25 years) and on a prevailing tendency to affect several males in the same family and, much more rarely, females. Thus in a number of affected fraternities, of 537 sons who grew up 390, or 72.6 percent, were known to be affected; whereas in 428 matured daughters of the same fraternities only 32 daughters, or 7.5 percent, were affected (table 1). Of the affected, 92 percent were thus males and 8 percent females. Again Wilbrand and Saenger (1913) found in 308 affected cases 272 males and 36 females, or 88 and 12 percent respectively. The population of persons affected with opticus atrophy is divided into males and females roughly in the proportion of 9 to 1.

The diminution of vision usually proceeds farther in the case of opticus atrophy than in the case of narcotic amblyopia, so that fingers can not be counted at a greater distance than 3 meters. In narcotic amblyopia vision is usually reduced one-half. But the best diagnostic criteria of Leber's disease is its hereditary quality.

Incidentally it may be mentioned that biotypes of hereditary opticus atrophy seem to occur. Some biotypes are characterized by early onset (at 8 or 10 years); others by prevailingly late onset (35 to 50 years). Some biotypes are characterized by cessation of degeneration at an early stage—with persistence of slight amblyopia; others by practically complete blindness. Apparently there are biotypes in which the heterozygous female tends to show opticus atrophy. The existence of the biotypes reminds one of allelomorphic series, of which the more nearly normal representatives are dominant over the more defective.

The enormous predominance of males early led to the conclusion that Leber's disease is a sex-linked one.

In typical sex linkage the percentage of incidence of the female sex is equal to the square of the incidence of the male sex. The reason for this is that while X′ indicates the incidence of the single affected sex chromosome that causes the sex-linked trait in (1X) males, X′X′ indicates the percentage incidence of two affected X′-chromosomes necessary to the production of 2X-females who show the sex-linked trait. Nobody has computed precisely the proportion of mature males in the native male population who have optic atrophy. Assume it as .005, or 5 per thousand of the population, then the proportion of females would be 25 per million. In other words the affected females would be 1/200th as common as affected males. The tables that I have collected contain about 75 affected females and 481 affected males. However, not all of these females have been seen. FLEISCHER and JOSENHAUS found in the literature only 6 cases of females that had been directly investigated. But KAWAKAMI (1926, p. 576) has the opinion that in Japan the incidence of females is much higher than in the European cases considered by FLEISCHER and JOSENHAUS. In any case, in the selected families affected females are about 1/10th instead of 1/200th as numerous as males. This result may be due to the expression of the trait in many heterozygous females.

Let us now consider the incidence of affected males and females following given matings in which affected X-chromosomes are probably involved.

The question has been frequently raised whether optic nerve atrophy follows the law of NASSE, like color-blindness; or the law of LOSSEN,

according to which an affected man has no affected descendants in first, second, or later generations (unless intermarriage occurs with females of affected stock).

Tables 2a to 2e contain data drawn from the pedigrees given for families whose defect is most probably true Leber's disease. In selection of families use was primarily made of the critical examination of DREXEL (1922). To DREXEL'S accepted cases are added certain earlier ones not considered by him and a number of families that have been published since his work. KAWAKAMI (1926) has published pedigree charts for a lot of cases that had appeared in the Japanese literature and had been overlooked. These I have not included. Most of them are fragmentary and, in general, the incidence of affected females is so high that they constitute a class quite different from the European and North American cases. I have, however, included KAWAKAMI'S own case. One wonders whether the Japanese physicians have a somewhat different criterion of Leber's disease from the European or whether the factor, or factors, that make for hereditary opticus atrophy lie in different chromosomes in the peoples of the two continents.

Considering this tabulation it appears that in pedigrees where 50 percent of affected males are expected (the mother being a conductor) 63 percent and 66 percent are found in matings I and IV respectively. The unexpectedly large proportion of affected males may be due to a selection of data: namely, of just the affected brothers, the others being unreported. In the type of mating (II) where the mother is affected and therefore 100 percent affected males are expected—73 percent are found. This result might be interpreted to indicate that some of the affected mothers are only heterozygous.

In matings (I) where the father is normal and the mother a conductor, no affected daughters are expected, but 6 percent are found, clearly indicating that some heterozygous daughters are affected, even though atypically. Where the father is normal and the mother is affected (mating II) the proportion of affected daughters rises to 17 percent. In mating III (affected father, genotypically normal mother) 2.8 percent of the daughters are affected. These results are irregular. They suggest that either there are biotypes in which the heterozygous female is affected; or else a special accessory factor for blindness exists in some strains.

In mating III, where the father is alone affected, there are very few sons affected. In the 2 matings that yield affected sons the mothers are really unknown. Though they were almost certainly not affected they may readily have been conductors. In GINSBERG'S family an affected man had

3 sons by one woman and 1 by another, all affected. We know nothing about these women though they were probably not affected. For all we know to the contrary they may have been sisters and both conductors. In the other families, comprising together 81 grown sons, none are affected. In view of our ignorance of the mothers the results of mating III are not opposed to NASSE'S law.

Again, KAWAKAMI (1926, pp. 592–594) has tabulated the best known families with optic nerve atrophy, with special reference to the vision of the mother's father of an affected person. There are 56 such mother's fathers described and 47 not described. Only 4 are known to have been blind. KAWAKAMI contrasts this condition of not more than 7 percent with the 40 percent occurrence of known color-blind mother's fathers in color-blind families. This difference is the more striking since the proportion of known to actually atrophically blind is doubtless greater than the proportion of known to actually color-blind. The 4 cases of maternal grandfathers affected with optic atrophy may well be due to inheritance from the mother's mother as a conductor. The fact of much higher incidence of affected maternal grandfathers in color-blind families than in families with optic nerve atrophy is strong evidence that inheritance does not follow the same law in both cases.

MACKLIN (1927), despite this evidence, or perhaps without fully considering it, is inclined to doubt the validity of LOSSEN'S law in opticus atrophy. She points out that usually too few generations are known or there are no male descendants of daughters of the affected man. This criticism is all too true. Still there is a remarkable absence of daughters of men with opticus atrophy who are certainly conductors. Referring to mating III, we find that in the family of USHER (1927) of 3 daughter's children of the blind grandfather not one was affected, although apparently of the age of incidence. Again in the family of HIRSCH (1923) the 3 sons of 2 daughters of an affected man (II 1) are unaffected; and again the married daughter of blind III 8 had 3 grown sons of whom none was affected. Also, of 5 other married daughters none of the 3 sons was affected.

Out of the hundreds of grandchildren of men with opticus atrophy the only sure cases of daughters' sons with opticus atrophy that I have been able to find in the literature (not explicable by the female lines) are the following:

In GOULD'S (1893) case, in the first generation there is a man with opticus atrophy one of whose daughters (II 4) had 4 sons who survived to maturity and one of these (III 9, who died at 40) had opticus atrophy (figure 2).

In HANCOCK's (1908) case a man (I 1) who had opticus atrophy had a normal daughter (II 1) whose 3 sons (III 1, 5, 8) all had opticus atrophy. She had a daughter also (III 3) who had 4 sons of whom 1 had opticus atrophy. A sister (III 7) of the last mentioned daughter's daughter had 2 affected sons. II 1 had another daughter, III 2, and her daughter (IV 3) had an affected son V 2 (figure 3).

These two families offer remarkable exceptions that only enforce the general rule that in typical Leber's disease affected males have no affected descendants. On the chromosome theory of inheritance, as indeed applied by KAWAKAMI (1926, p. 590), the union of a Y-chromosome with the

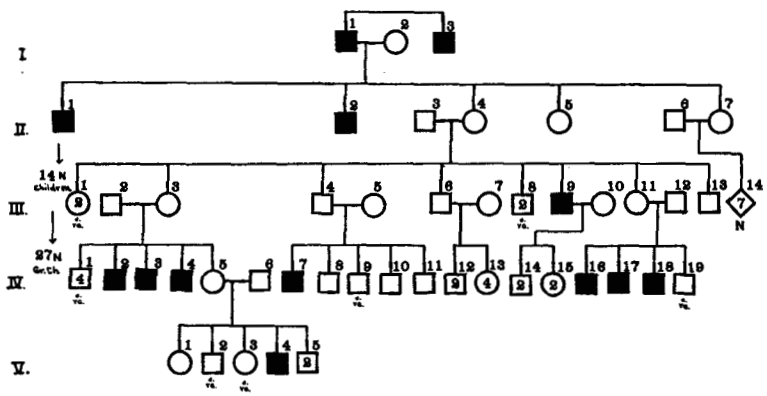

FIGURE 2.—Pedigree of opticus atrophy, by GOULD, 1893. II 1, age at onset unknown; became blind from same type of disease which has since appeared in the later generations. His father was blind and deaf somewhat late in life. I 3 affected at 28 years, like his brother. II 1 affected, died at 86. II 2 affected at 28. II 4 eyes weak and watering; but not blind, died at 62 years. II 5, horned in eye by a cow; blind before 40. II 7 became blind late in life, cause unknown (probably cataract); no affected children. The later generations follow the rule of sex-linked inheritance; except that IV 7 offers difficulties since his sex chromosome was derived from his mother who, apparently, does not belong to the family with opticus atrophy.

affected X-chromosome from a female conductor permits, indeed, the optic nerve atrophy to develop in the male. But somewhere in the development of the zygote or of its sex cells, or during maturation the affected X-chromosome becomes either modified or lost. Or it may be that the sperm cells that carry the affected X-chromosome do not function. At any rate, in the vast majority of cases the affected X-chromosome that has been associated with the Y-chromosome does not function again. Of course, if daughters of affected males produce no conductor-daughters; or such daughters produce few, or no, sons the same result would follow. In the families of GOULD and

of HANCOCK considered above the Y-chromosome does not experience its usual, but peculiar, fate.

Finally, there are a few families in which inheritance of optic nerve atrophy appears to follow a non-sex-linked and nearly, or perfectly, a dominant type of inheritance. The case of KNAPP (1904) is an example. Here an affected father has 2 affected sons out of 5; and 2 affected daughters out of 3. One of the affected daughters marries her normal cousin and they have 4 affected sons out of 5 and 1 unaffected daughter.

Again, WAARDENBURG (1924) tells of a family in which the grandfather, who was examined ophthalmoscopically, showed optic nerve atrophy. His daughter (also observed ophthalmoscopically) had a similar loss of

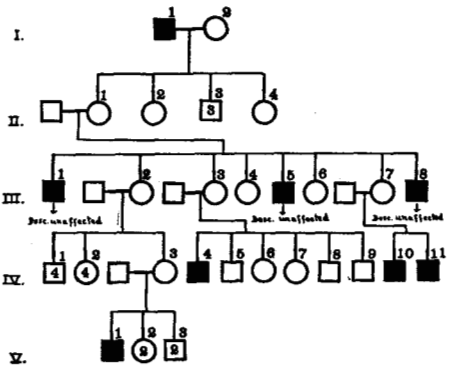

FIGURE 3.—Pedigree of opticus atrophy, by HANCOCK, 1908. I 1 in third decade sight failed; later improved; lived to be 100 years old. III 1 vision failed in both eyes at between 20 and 30 years; never recovered, a heavy smoker. III 5 lost vision like III 1; after a year recovered sight; no abuse of alcohol or tobacco. III 8 attacked at between 20 and 30 years; not abstemious; no recovery. III 1 had 4 sons and 3 daughters, and he had 5 grandsons, none affected at the time of report.

vision. By a normal man she has 5 sons, 3 affected; and 5 daughters, 1 affected. This looks like a case of a dominant gene (instead of a recessive) located in an autosome (instead of X-chromosome). Genetically it is as different from ordinary Leber's disease as can well be.

KROPP (1927) described a family in which the father began to lose vision at 21 years, having a partial opticus atrophy on both sides. His wife, so far as all tests go, has normal vision. They had 5 children. The first son and first daughter had normal vision. The second daughter had a neuritis back of the eyeball of unexplained etiology, and on both sides a central scotom. The third daughter had atrophic optic nerves, with relative central color scotom, on both sides. In this case the genetic condition is like that in WAARDENBURG'S case cited in the last paragraph.

WAARDENBURG (1924, Stammbaum IV, V) gives two pedigrees where the marriage of unaffected first cousins has resulted in affected sons and daughters. These pedigrees suggest that the gene concerned is a recessive, autosomal one.

These aberrant cases are quite confusing. That a recessive, sex-linked gene might come to lie in an autosome is quite possible. A similar exchange of genes between non-homologous chromosomes has been described in Datura (BELLING and BLAKESLEE 1926), and elsewhere. That a gene responsible for continued functional vigor should in some cases by "weakness" (recessiveness) produce opticus atrophy and in other cases by "strength" (dominance) produce likewise the same type of opticus atrophy seems incredible. Possibly just a delicate median balance of functional activity of this gene is required for normal functioning of the optic nerve.

The conclusion of this analysis of the cases of Leber's disease is that it is generally a recessive, sex-linked trait with a usual failure to reappear in descendants of affected males. However, it is expressed occasionally in females who are "conductors" or heterozygous for the trait. Moreover, the trait of hereditary opticus atrophy is sometimes induced by a gene that is not located in the sex-chromosome.

OTHER SEX-LINKED TRAITS

Brief mention may be made of other sex-linked traits. No attempt is made here to analyze them or to extend the bibliography.

Hypoplasia of white brain substance, as worked out by MERZBACHER (1909), seems to be a case of sex-linkage, but so far confined to one family.

Night blindness, or hemerolopia of the sex-linked type, occurs in which males only are affected. This is not to assert that females can not be affected—the available pedigrees are very few in number. BELL (1922) lists only the great CUNIER-TRUC-NETTLESHIP pedigree, that of NETTLESHIP and MORTON and 29 minor ones. The large CUNIER-TRUC-NETTLESHIP pedigree of the NOUGARET family of VENDÉMIAN includes both males and females. There are 12 families in which the males only are affected. AMMANN'S (1898) case is typical, with 14 affected males and no affected female. All affected males inherit through unaffected females. Incidentally, all affected males are said to be myopic, but this is based only on family tradition.

Myopia, or short sightedness, in some families, runs a sex-linked type of inheritance. Thus, in some of the night-blind families with affected males only there is also myopia in some (or all) of the affected males. Even without night blindness some families have been described, like

those of WORTH (1906) (see figure 4) and OSWALD (1911), in which males alone are myopic and inherit through unaffected females.

A sex-linked inheritance of megalocornia has been described by KAYSER (1914).

Pseudo-hypertrophic muscular paralysis of GOWERS (1879) is also sometimes sex-linked. In sex-linked families about 6 times as many males are affected as females. TSCHERNING (1921) has discussed inheritance in this disease.

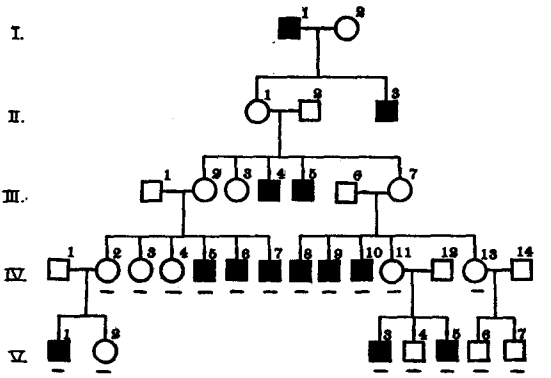

FIGURE 4.—Pedigree of family with hereditary sex-linked myopia (WORTH 1906). The black symbols indicate myopia. The underscored symbols represent persons examined. In addition some members of the IIId generation were seen. The other cases are classified on the basis of statements of relatives. The myopia was measured as 10 or 12 D, with some astigmatism.

Other traits for which sex-linkage, in certain strains, has been found are: coloboma, nystagmus, microphthalmia, ichthyosis, webbed toes, toothlessness, deficiency in sense of smell and wanderlust, or nomadism.

SOME NEW PEDIGREES OF HAEMOPHILIA

During the summer of 1927, under a grant from the Research Committee of the AMERICAN MEDICAL ASSOCIATION, Mr. C. V. GREEN undertook to trace families with haemophilia in order: (1) to check on them the method of inheritance and (2) to learn if in any of these families there was also color-blindness. The special purpose of the investigation was to find evidence of sex-linkage of these two characters.

Mr. GREEN took preliminary instruction in the determination of haemophilia from Professor W. H. HOWELL, to whom we desire to express our gratitude. For determination of color-blindness the Stilling Isochromatic plates were used. Mr. GREEN's itinerary took him to Dushore, Athens, Sayre and Wilkesbarre, Pennsylvania (July 12–15), to Findlay and Day-

ton, Ohio (July 18th and 19th), to Rushmore, Minn. (July 25), to Sibley, Iowa (July 26), to Frederickton and Des Moines, Iowa (July 28–August 1), to Williamsport, Pennsylvania (August 15), to Cleveland, Ohio (August 30, 31) and to Detroit (September 2). A considerable amount of time was spent on trips that yielded no result, owing to the removal of families.

R-family (figure 5)

The most extensive series of families included certain descendants of the well-known MOLYNEUX strain of Pennsylvania. A MOLYNEUX daughter married a distant cousin of the same MOLYNEUX stock and by him had 4 sons, half with haemophilia (II 3, 5) and 2 daughters (II 7, 8). A sister of the husband mentioned in the last sentence had 1 son (II 9), a bleeder.

II 3 lives in Wilkesbarre. At about 10 years of age he cut his finger badly and it was then first discovered that he was haemophilic. He has

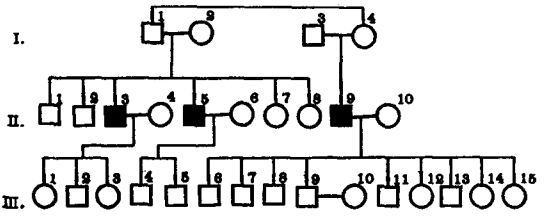

FIGURE 5.—R. family with haemophilia. The black squares indicate bleeders.

been twice given up to die by physicians, as a result of bleeding from extracted teeth. He has not been troubled lately as he takes very good care of himself (own statement). He was given the Stilling test and proved to have a very good color discrimination, much better than his wife's. One of their sons was given the Stilling test and did exceptionally well in it.

II 5 (brother of II 3) works at Athens, Pa. He has been in the hospital at Sayre on two or three occasions from hemorrhages, one of which was caused by a rather severe bruise on the shin. Blood collected until a large black lining was formed. When this was lanced a severe attack of bleeding followed. II 5 did only fairly well on the Stilling test; but quite as well as II 3's wife.

II 9 (cousin of the foregoing) is a well informed farmer, living near Dushore, Pennsylvania. He appreciates the method of inheritance of haemophilia. His worst attack of bleeding resulted from an infected finger, followed by "blood poisoning." On this occasion he nearly bled to death. His teeth are in bad condition but he hesitates to have them extracted,

fearing the probable consequences. He did fairly well on the Stilling test; better than his wife. Three of their 9 children, who were tested, did well.

The distribution of haemophilia in this family accords with the law of sex-linked inheritance of haemophilia; a typical sex-linkage confined to the male sex. None of the offspring of affected males are affected. Presumably the consorts of the affected males are genetically normal. There is no color-blindness in this family.

M-family

This is also a branch of the MOLYNEUX family, I 2 having been a MOLYNEUX before marriage. She had 7 sons. Of these 2 are known to have been haemophilic. II 8 was seen. He is affected by slight shaving cuts no more than is a normal person. His worst attack occurred about a year ago when he had his teeth extracted. At that time he was confined in a hospital at Sayre, Pennsylvania for a considerable period. It was feared that the hemorrhages would be fatal.

The color discrimination of II 8 is good, as good as that of his wife. Also the color discrimination of his daughter III 1 and son III 2 in each case is good—about the same as in the mother; the 9 year old sister made 2 more errors than her 7 year old brother.

P-family

The propositus, I 1, is a member of the MOLYNEUX family and lives in Detroit, Michigan. He is a pale, sickly man. His teeth are in very bad condition but he does not dare to have them extracted. He is troubled much with rheumatism. The slightest bruise causes swellings at the joints, especially at the knees and elbows, which are distended almost constantly. A slight cut on his hands causes a great amount of bleeding. When he was a child his mother had to watch at his bedside day and night for six weeks, as a result of having a milk tooth extracted. As a child he had an arm broken which could not be set right because of the excessive bleeding. According to his sister his whole life has been ruined on account of his defect. His case is the most severe of any seen among the MOLYNEUX. His color discrimination was not tested.

A-family

In this family, also one of the MOLYNEUX strain, the wife, I 2, is a sister of I 1 of the P. family. She married an unrelated man. They have 2 sons, ages 20 and 9 years respectively, and a daughter, aged 7. The second son, II 2, has haemophilia. He was first discovered to be a bleeder

when about 5 years of age. He had a deciduous tooth extracted and there was profuse bleeding for 9 or 10 days; a serum was successfully used to stop it. Bleeding at the mouth has several times occurred, especially around the teeth; and his pillow is sometimes badly stained with blood, or he has to leave school on account of bleeding at the mouth. Cuts on other parts of the body do not trouble him greatly. He bleeds from them hardly more than a normal person. He is not yet, at 9 years, troubled with swellings at the joints.

None of the family were color-blind. The largest number (about 13) of errors (Stilling test) was made by the 7 year old girl.

Gross family

The pedigree of this family is given in figure 6. It is the family to which most attention was paid. It is the only one in which color-blindness was certainly combined with haemophilia.

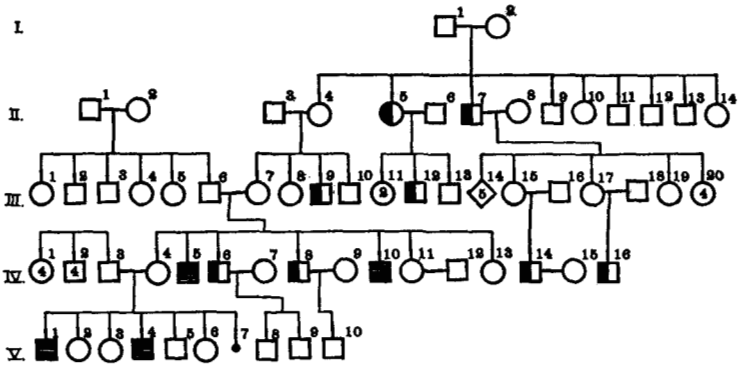

FIGURE 6.—Pedigree chartof the GROSS family in which both haemophilia and color-blindness occur. Color-blindness is indicated by the half-black symbol and haemophilia by the horizontal stripes. It will be noted that haemophilia is not found back of generation IV, while color-blindness occurs in generations II, III and IV. The two conditions are not combined in any one person.

III 7, the mother of the color-blind and haemophilic fraternity, stated that the haemophilic members of this family have always been recognized as such when only a few months old, in this respect differing from the MOLYNEUX family. Later they acquire painful swellings at the joints, originating even from only a very slight bruise.

III 7 has had 7 children, 4 boys and 3 girls. None of the girls were affected somatically, though the eldest has had 2 affected sons out of 3. Of III 7's children, IV 5 died in infancy from bleeding from a cut in the mouth made by a piece of glass.

IV 6 shows no symptoms of haemophilia. He was tested for color discrimination and was found to be color-blind.

IV 8 also shows no symptoms of haemophilia and is also color-blind. Thus both failed completely on the Stilling test group 2; also groups 4, 5, 6, 7 and 8, except that II 6 got 3 figures right out of 16, in the group 6 test. They made such errors on the group 9 test as to lead to the suspicion that they carried diminished susceptibility to red.

These two persons are the only ones in the immediate family, so far as studied, who showed color-blindness. In their mother's family color-blind persons (male only) occur as follows: Her brother, III 9; her aunt, II 5 (doubtful); this aunt's son, III 12; aunt's brother, II 7; and 2 of his daughters' sons, IV 13, IV 15.

There are no cases of color-blindness on the father's side of the house. Accordingly we may conclude that the gene for color-blindness was carried in the X-chromosome—as that is derived by sons from their mother's side only.

In the main fraternity there is one other male, brother of the color-blind men, who has haemophilia. IV 10, DANIEL G., is 28 years old, and had a bad spell about 3 months previously. These attacks resemble rheumatism, and have followed bad sprains of which he was, at the time, unaware. At other times he can do heavy work and not be troubled. ALFRED V 1 is the same way. When DANIEL was in the army hospital he had his ear pricked and it bled so profusely that his shirt became covered with blood. This came as a surprise to the physicians who a short time previously found that a finger prick was not followed by excessive bleeding.

In the fifth generation are two children, V 1 and V 4 who have a history of bleeding. V 4 died recently from pneumonia and bleeding. V 1, at 19 years, is tall and anemic. At the time of Mr. GREEN'S visit in August, 1927, he was just recovering from a strain of some kind and had been laid up for 3 or 4 weeks. All of the other children look healthy.

Color tests were applied to the mother (IV 4) of the fraternity described in the last paragraph. She made only a few errors until she came to group IX, 2. In this group of 4 characters she attempted only 1, and this was correct. She made only 1 error with group IX, 1 and one error in group X, 1 and 2. She apparently has a trace of blue-green blindness.

Color tests were applied to the four oldest members of the fraternity of the haemophilic boy (V 1). He himself has remarkably good color discrimination, much better than his mother's. He made only one error in reading the 30 plates. V 2 ♀ made only one slight error. V 3 ♀ made only the same single error that her sister did. V 5 ♂, apparently about 6 years

old, made 14 errors. Especially did he fail in group IX—the test for blue-yellow. As this age may be too early for entire color discrimination capacity to be functional one can not conclude that any of the children are color-blind.

B-family

This is a branch of the MOLYNEUX family, the connection being through I 2, who was evidently a conductor. She had 10 children, 6 sons and 4 daughters. Four of the sons had haemophilia. Of these sons II 8 alone survives at the age of 70 years. He seems well preserved and looks normal, He was about 10 years old when it was first discovered that he was a bleeder. Later he had a permanent tooth pulled and it bled so badly that his pillow would be soaked in blood. Cuts and bruises sometimes trouble him. From a bad bruise on the shin he was confined to bed for 3 or 4 weeks. With the Stilling plates his color discrimination appeared normal.

II 8 has had 5 daughters and 1 son, all without haemophilia. Two full sisters of II 8 have respectively 1 son out of 2 and 1 out of 3 who are haemophilic.

III 2, daughter of II 8, has 3 sons, all haemophilic and 1 daughter. She herself has no bleeding tendency. She made 8 errors in the Stilling plates, all in miscalling a 3 an 8.

All of her sons are, as stated, badly affected with bleeding. One of them plays football and his bruises are terrible to see. Cuts cause all of these boys trouble. IV 5 was seen. He is a fine, normal appearing boy, tall and large for his age. His color discrimination is good.

G-O family

This is a branch of the MOLYNEUX family. I 2 was a PARDOE, allied to that family. She has a son who has haemophilia; also a daughter, aged about 12 years.

III 1, R.G., at 23 years is well conditioned but somewhat pale. He has had 3 bad attacks of haemophilia: (1) At 10 years he bumped his forehead. After seeming to heal, the wound, on the ninth day, broke out again. He was confined to his bed on this occasion. (2) At about 15 years he cut his foot on glass. After the blood flow was staunched it broke out again after a week, or 10 days; but he did not have to go to bed on account of it. (3) About 2 months before the interview he had a lower molar pulled. He was laid up for about 2 weeks. Treatment with horse serum worked satisfactorily. The young man has often had to stop nose bleed by the

use of a calcium compound, perhaps calcium lactate. He has good color discrimination, as shown by use of the Stilling test.

Pol family

This is a Ukrainian family, living in Cleveland, Ohio. The father, I 1, is dead; the mother, I 2, is about 25 years old. She is not a bleeder and can not find, after inquiry, any other cases of bleeding in the family. She has good color discrimination, confusing only 3's for 8's.

Her eldest son is 10 years old; and looks pale. He has had 4 bad periods of bleeding and has been in the hospital for them. At the time of Mr. GREEN'S visit he was in the hospital due to a cut under the tongue from a piece of iron. A vesicle of blood under the tongue, size of a bean, was cauterized and removed. He had 4 transfusions of blood from his mother during about 2 weeks, the amount of transfusion being about 100 to 300cc; and the infusion was temporarily successful. The boy was recovering.

By Stilling's plates the mother read all figures correctly except for calling five 3's eights. The son, NICHOLAS, could not read the figures of group IX. Also most of the figures at group VI, especially 1 and 4, could not be read. The sister, aged 9, made a few errors which may be due to her immaturity. It seems probable that NICHOLAS carries 2 sex-linked defects; haemophilia and color-blindness.

Car family

In this Cleveland family the mother was interviewed by telephone through Doctor C. W. WYCKOFF'S cooperation. This mother, who is herself free from haemophilia, has 2 living sons and had 2 others who died in early infancy. The family has been traced back for 5 generations and no case of haemophilia found previously. The elder son was discovered to be a bleeder at 6 months. He has been repeatedly troubled with bleeding and has had 5 blood transfusions; clotting time before transfusion 9 minutes, after transfusion 6 minutes. There are swellings at the joints and blood extraversations; but the lad seems to be getting better. The younger son was also a bleeder. If he bit his tongue or lip, the hemorrhage would persist for days. Clotting time 9–1/2 minutes.

Nor family

This Cleveland family was not seen but the haemophilic son of about 6 years was known by Professor T. WINGATE TODD of the Department of Anatomy, WESTERN RESERVE UNIVERSITY and Doctor DAVIS of the CITY HOSPITAL to be haemophilic.

Nar family

This Cleveland family was visited by Mr. GREEN. The father (H.S.N.) says he bleeds badly—though not so much of late. The worst time he had was when his teeth were extracted, for there was great difficulty in stopping the flow of blood. Of the mother's family little is known.

There is a daughter, MARGARET, aged 8 years. When she was a baby she was diagnosed by Doctor T. B. SMITH as a case of haemophilia. She has never had swellings at the joints. Doctor C. W. WYCKOFF finds her blood-coagulation time to be 15 minutes, and the coagulation is then not typical. A tonsil operation having been decided on she was given calcium lactate, 10 grains 3 times a day for 1 month prior to the operation. Her coagulation time was reduced to 5 minutes. Despite every precaution in the way of ligation of vessels the operator had a great deal of trouble for 10 or 12 hours in controlling the hemorrhage.

There are 2 sons, aged 4 and 2 years. It is early to say whether or not they are haemophiles. Doctor WYCKOFF states that they bleed very easily and for a long time after minor injuries, but their joints do not show swellings or blood extraversations. No color tests were made on this family.

CROSSING OVER IN MAN

Since there are several known sex-linked characters in man it is natural to look for crossing over. Crossing over in the children might be found in cases where a female with at least two sex-linked genes was mated with the "normal" male. These conditions are not easy to meet, since sex-linked phaenotypic traits are relatively uncommon in females. But the conductor female can be inferred from her relationship to affected males. It is possible that crossing over might be found when the male carries 2 sex-linked genes. But in view of the relative inactivity of the Y-chromosome in man, as in Drosophila, it is to be expected that in the human, as in Drosophila, there may be no crossing over in the male.

In Mr. GREEN'S study an attempt was made to find a person, either man or woman, who bore two genes for recessive, sex-linked traits. Haemophilia and color-blindness seemed the most promising. The GROSS family, indeed, showed both traits—in males only. But in this family no individual showed both traits. In the GROSS pedigree, III 7 is the sister of a color-blind man and her mother has a color-blind brother and the mother's sister has a color-blind son. This incidence of color-blindness in near relatives supports the conclusion from her progeny that she carries the color-blindness in one X-chromosome. III 7 transmits haemophilia to half of her sons and, accordingly, we conclude that she carries the gene

for haemophilia in one X-chromosome. The X-chromosome carrying color-blindness and the X-chromosome carrying haemophilia are apparently not the same X-chromosome. One might hastily suppose that if III 7 got the X-chromosome with the color-blind gene from her mother's side, she got that carrying the gene for haemophilia from the father's side. But, if so, the father would be haemophilic. But SIMON GROSS (II 6), her father, was seen and there is no doubt that he is free from the bleeding tendency, for his blood clotted in 1 minute. (GRACE ALLEN: E.R.O,. A 8102–25).

Accordingly we are forced to the conclusion that both genes for color-blindness and haemophilia are carried in the X-chromosome that the mother (III 7) received from her mother or else that this X-chromosome underwent mutation in the haemophilic gene in III 7. Had the haemo-

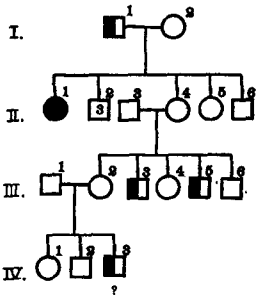

FIGURE 7.—Pedigree chart of a family with haemophilia combined with color-blindness (MADLENER 1928). I 1 both haemophilic and color-blind. II 1 (his daughter) is haemophilic III 3, 5 both haemophilic and color-blind. IV 3, certainly haemophilic and possibly color-blind.

philic gene been in the X-chromosome that III 7 received from her mother and which carried the color-blind gene we might expect haemophilia in III 7's brothers or her sister's sons, or those of her mother's sisters. III 7 had 2 brothers neither of whom was a haemophilic while 1 was color-blind. III 7 had 1 sister whose 2 sons were normal. III 7's mother had a color-blind brother but no haemophilic brother, out of 5 brothers. One sister had 2 sons, 1 color-blind. The other sister had 1 daughter who had 2 sons, not affected, and 3 daughters 1 of whom had 9 sons unaffected. The pedigree suggests that the haemophilia mutation had occurred in the paternal X-chromosome, while in the ovary of III 7.

The possibility that 2 sex-linked traits occur in the same individual has actually been realized in the remarkable German pedigree recently published by MADLENER (1928) which starts with one, H. DÖRR (figure 7). He (I 2) was a haemophilic and also color-blind. He had 7 children, of

whom 1 son was haemophilic and 1 daughter a conductor (to her 2 sons) of both haemophilia and color-blindness. In this case the sex-chromosomes of the mother of the 2 affected sons carried both a gene for haemophilia and one for color-blindness. Also a daughter of this mother certainly carried the gene for haemophilia and perhaps that of color-blindness (her 4 year old son is haemophilic but a little too young to be sure of his inability to distinguish colors). In this family, then, the linkage of 2 sex-chromosome genes is clear. Since the number of offspring is small it is not significant one way or the other that there is no evidence of "crossing over."

The pedigrees of AMMANN (1898) and of PFLÜGER (1881) published by BELL (1922) show no crossing over between night blindness add myopia and in the case of NETTLESHIP (BELL'S figures 319–320 and 323) the incidence of these two traits is irregular. The cases of PAGENSTECHER (BELL, figure 318) and CUTLER (figure 325) are too fragmentary to permit of any conclusion as to the rate of crossing over.

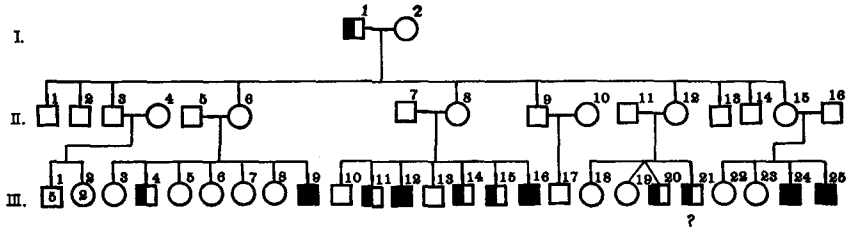

FIGURE 8.—Pedigree chart of a family combining night blindness and myopia (NEWMAN 1913). I 1 probably night blind and myopic. All symbols that are wholly black indicate night blindness without myopia; symbols that are half black indicate night blindness combined with myopia. There is doubt whether or not III 21 is myopic.

Instructive in the matter of crossing over is the pedigree given by NEWMAN (1913) and reproduced, in part, in figure 8. The significant individuals are described as follows:

I 1 at report 74 years old, night blind from infancy, "short sighted" (probably myopic). His six sons and four daughters are all normal. Of these children II 3 is not night blind or myopic and none of his 7 children are affected. II 6 is unaffected but is a conductor since both of her sons are night blind. III 4 "was unmistakably night blind and showed the usual associated defects" which the "Treasury of Human Inheritance" interprets as showing myopia. We have followed the "Treasury" in this interpretation. Thus the grandson had both the sex-linked traits of his grandfather. III 9 is typically night blind at 4 years. His sister, a university student of zoology, writes: "Brother can not see anything out of the light at night except that on bright nights he can see anything between

him and the sky." (Windmill, trees, houses, etc.) "He could not distinguish his express wagon, his kitten or other objects on the ground." "He is not short-sighted at all." In this case, then, only one of the two sex-linked defects was received by the night-blind son.

II 8 (Mrs. UZZELL) had 7 sons, III 10–16. III 10 is normal. III 11 is night blind, myopic and strabismic. III 12, at 13 years, is "night blind, without any other optic defect." Here again one of the sex-linked traits is lost. III 13 is normal. III 14 at 8 years is night blind, myopic and strabismic. III 15 at 6 years is likewise night blind, myopic and strabismic. III 16, at 4 years is night blind, but without other associated defects.

II 12 (Mrs. E. F. FLOYD) has had 2 sons, both night blind and 2 daughters normal. III 20, at 5 years, is clearly myopic and strabismic. The evidence is less clear that he is night blind.

III 21, now dead, "lived long enough to exhibit sure signs of night blindness. No facts about associated defects."

II 15 ♀ had 2 daughters and 2 sons. III 24, aged 4, is "night blind, but without other defects." III 25, aged 8 months at time of report, "shows unmistakable signs of night blindness, but no other defect." These two cases would seem too young for a critical statement.

To sum up, III 12, at 13 "night blind but without any other optic defect," a first cousin of the intelligent, trained reporter, is one clear case of inheritance of one of two genes linked in the mother's father. III 9, III 16 and III 24 are night blind but still too young for it to be certain that they are myopic. No case of myopia without night blindness occurs in this fraternity. However, the chance of failure to get just this condition is considerable.

That such a segregation of myopia from night blindness is possible is indicated in pedigree No. 325 of the "Treasury." In the latest generation of a night blind family one of 4 brothers shows night blindness and myopia. His eldest brother at 28 years had myopia of 9 D, but no night blindness. Their mother had 2 brothers. Of these 1 died at 9 years, night blind, but nothing is said about refraction. The other brother seen at 46 years was night-blind. His vision was poor but myopia is not mentioned. As the mother has a myopic (and night blind) nephew it seems highly probable that she carries both defects in one of her X-chromosomes and that crossing over has occured in the gamete that went to form the eldest son.

We may conclude from these still incomplete facts and considerations that there is good evidence of crossing over in sex-linked characters of man. There is then in this phenomenon also no distinction between the genus Homo, Drosophila among insects and some flowering plants.

DISCUSSION

A review of sex-linked characters in man yields something of a surprise that in a species whose traits have been so long analyzed as man's there should be so few clear-cut sex-linked characters known. In Drosophila perhaps a hundred sex-linked characters have been determined. To be sure, there are only 4 pairs of chromosomes in Drosophila where there are 24 in man but even this fact does not account for the difference.

Another genetic difference between man and the insect is that while in the latter the sex-linked characters are mostly simple and clean-cut most of the sex-linked characters in man are so complex that their genetic behavior is not obvious. Red-green color-blindness alone seems fairly simple. Haemophilia is lethal when duplex and optic nerve atrophy, even if we eliminate the obviously non-genetic forms, shows many irregularities, such as the usual failure to reappear in the sons of daughters of affected men.

An interpretation of the confusing nature of sex-linked inheritance in man is to be sought, I conclude, in the same causes that are responsible for the generally small number of simple clean-cut genetic traits in man. Eye color and albinism, defects of eyes and appendages and Huntington's chorea among nervous diseases are the genetically simplest traits. Most traits, like pigmentation of skin and hair, aberrant proportions of body, and other bodily defects, mental traits of most sorts, and the susceptibility to many diseases, have a very complex genetic basis.

In general, it appears that man, perhaps just because he lies at the end of the most highly differentiated of evolutionary lines, has accumulated more mutations than any other species. Mutations have been added to preexisting mutations of the same organ. Also, it is probable that through translocations the same gene has been transferred, perhaps repeatedly, from one chromosome to another so that a gene is sex-linked in some strains and not in others. And, possibly through new relations to other genes, a trait that is recessive (or unexpressed in the heterozygote) in one strain becomes dominant (expressed in the heterozygote) in another. All of these possible complications have to be kept in mind in the study of human heredity. Probably in no other species is inheritance so complicated. This is not to suggest that the search for the inheritance factors in human traits has to be abandoned, but rather it has to be undertaken on a larger scale, with a greater expenditure of effort and funds. The importance to humanity of an understanding of the origin and development of human traits is so great, the issues at stake are so tremendous, that

research on a broader basis is urgently called for and would be wholly justified in its results.

NEED OF A REPOSITORY OF FAMILY HISTORIES

The study of sex-linked traits brings home very vividly to the geneticist the many difficulties in the study of human genetics. One of these is the time elapsing between the human generations. If the observer is a young man, of say 30 years, he may hope to observe the young children of a family, their parents and one or more grandparents, also collaterals. Such a young observer may, under fortunate conditions, see these children grow to maturity as he himself progresses toward old age. He may, before he dies, observe these children's children. Thus, under the most favorable conditions, he can see two complete mature generations; one incomplete one (of the grandparents) and one of immature individuals. For the study of inheritance of some characters this may suffice; but these favorable conditions are, alas, rarely realized. The observer wishes that, for his research, he had the contemporary physical and medical records of an earlier generation. But if any of them ever existed they have probably been destroyed. Then he regrets that there is no depository of medical and performance records about people (as there is about race horses and cows).

In the case of sex-linked traits, where a generation is regularly skipped, and 2 or more may be, this need is especially acute. An example will illustrate this need. Suppose we have observed opticus atrophy in a young man of 20 years, and we desire to know if it be of the hereditary type or not. The parents, now 40 to 60 years of age, are not affected. Of the grandparents probably half are dead and any medical records about them have probably been destroyed. We must rely upon the testimony of the "parents" and their siblings, if any, as to the condition of sight in the grandparents, use of narcotics, diabetic symptoms, etc. The record we get from the parents will often be very incomplete. Were medical records extant, how eagerly would they be examined!

Or the case may be that of two parents both affected with opticus atrophy. At the time of observation they have children of 10 to 2 years. How important to know the history of these children 10 or 15 years later! Yet the observing physician may in the meantime have moved or the family may have found a home elsewhere and there is no one to follow up the family and record the subsequent history of the children. Were there a depository, in which the full record with names and addresses might be preserved, then the early history would not be lost and a student of hereditary opticus atrophy might complete the medical history of the family

and draw important biological conclusions. It ought to be regarded as against the public interest to destroy medical records. Individual interests are, of course, to be considered and safeguarded; but the interest of the race should be regarded as supreme.

SUMMARY

The different sex-linked traits show differences in genetic behavior. Red-green color-blindness behaves like a typical sex-linked trait. Haemophilia is exceptional in that all duplex recessive female zygotes die. Optic nerve atrophy appears in several genetic types, only one of which is typically sex-linked, and in that type daughters of affected males rarely have affected sons. Female conductors form a genetic stolon from which affected males bud off. Also the incidence of opticus atrophy in females is unexpectedly high, probably due to the expression of the trait in the heterozygous condition.

Other sex-linked traits that are rare or less carefully analyzed are: hypoplasia of brain substance (MERZBACHER), night blindness (or hemeralopia), some strains of myopia, pseudohypertrophic muscular paralysis of GOWERS, and megalocornia. To these traits wanderlust or nomadism may be added. Still less well documented are coloboma, nystagmus, microphthalmia, ichthyosis, webbed toes, toothlessness and deficiency in sense of smell.

Since two sex-linked characters occurring in the same family should show linkage in inheritance such "double-recessives" were looked for. In a haemophilic family (GROSS) color-blindness was found, but the haemophilia appeared to be of such recent origin that linkage of its gene with that of color-blindness could not be studied. A family containing double recessive individuals (DÖRR) has been described. It is probable that the concurrence in some families of night blindness and myopia is due to sex-linkage. Crossing over between the genes of night blindness and myopia appears in the family described by NEWMAN, and more irregularly in a few others.

Finally the need of a repository of family histories to provide, in time, documentary evidence of traits of members of earlier generations—especially important in sex-linked traits—is stressed.

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TABLE 1

Incidence of hereditary optic atrophy in the offspring of various types of matings. N, normal; Con, conductor (heterozygous) female; Atrp, phaenotypically with opticus atrophy.

MATING		SONS				DAUGHTERS			
		Number		Percent affected		Number		Percent affected	
FATHER	MOTHER	Total less †yg	Affected	found	*expected*	Total less †yg	affected	found	*expected*
1 N	Con.	419	263	63	*50*	328	26	8.9	*0*
2 N	Atrp	26	19	73	*100*	24	4	17	*0*
3 Atrp	N	86	5	5.8	*0*	72	2	2.8	*0*
4 Atrp	Con.	3	2	66	*50*	1	0	0	*50*
5 Atrp	Atrp	3	1	33	*100*	3*	0	0	*100*
		537	390	72.6		428	32	7.5	

* These daughters are still young!

† Died young.

TABLE 2a

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating I. F, Normal; M, conductor.

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †vg	Affected		No	X or †vg	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
LEBER (1871) 1 fam.	I 3	5		5	100	1	0	1	100	..	..	a
LEBER (1811)+VOSSIUS (1900)+MÜGGE (1911). See DREXEL, 1922, p. 25.												
LEBER's IV fam.	II 2	4		4	100	2	..	0	0	..	..	
PUPALL (1876)	I 2	3		3	100	3	..	0	0			b
SCHLÜTER (1883)	I 2	1		1	100	2		0	0	1	50	
	I 3	3		3	100	1		0	0	1	100	
	II 2	1		1	100	1	1	..	..			
	II 4	1		1	100			..	..			
	II 8	2		2	100	1	1	..	..			
SCHLÜTER (1883)	I 1	3		2	67	1		1	100			c
	I 3	2		2	100	?						
LAWFORD (1887)	I 1	2		2	100	1		1	100			d
	I 2	3		3	100	4		0	0			
HASWELL (1888)	I 2	2		2	100	2		2	100			
	III 7	1		1	100	7		0	0			
BROWNE (1888)		3		3	100	2		0	0			e
SOMYA (1892)	I 1					2		0	0	2	100	
	II 1	2		2	100	0		..	..	..	..	
	II 2	3		2	67	1		1	100	..	..	
	II 1	0		..	..	3		0	0	1	33	
	III 2	6		4	67	5		0	0	..	..	
DESPAGNET (1892)	I 2	4		4	100	1		1	100	..	..	f
GOULD (1893)	III 3	5		1	20	5	2	0	0	2	67	
	IV 3	7	4	3	100	1	0	0	0	1	100	
	IV 8	4	1	3	100	0						
	V 6	4	1	1	33	1	0	0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	SONS					DAUGHTERS				CONDUCTORS		Remarks
	Reference to Mother	No.	X or two	Affected		No.	X or two	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
GOULD II (1893)	I 2	3	0	2	67	2	0	0	0	..	..	
WESTHOFF (1895)	I 2	2	0	2	100	1	0	0	0	1	100	
	II 2	3	0	3	100	1	0	0	0	1	100	
	III 2	5		4	80	1	0	0	0	..	..	
SNELL (1897)	II 2	4	2	2	100	5	0	0	0	..	..	g
LEITNER (1897)	I 1	3	0	3	100	1	0	0	0	1	100	
	II 4	4	0	3	75							
LEITNER (1898)	I 2	3	0	0	0	9		0	0	3	33	
	II 1	3		3	100	3		0	0	..	..	
	II 2	4		1	25	3		0	0	..	..	
LEITNER (1898)	II 5	2		1	50	7		0	0	..	..	
POSEY (1898)	II 7	2		1	50	3		0	0	1	33	
	III 3	1		1	100							h
RAYMOND (1898)	I 2	1		1	100	1		0	0	1	100	
	II 1	3		1	33	2		0	0	2	100	
	III 1	2		1	50	1		0	0	..	..	
	II 2	1		1	100	..		..	..	..	..	
	I 2	0		..	..	3		..	..	3	100	
	II 1	1		1	100	1		0	0	0	0	
	II 2	4		2	50	1		0	0	..	..	
	II 3	2		1	50							
HAWKES, (ERO) (1900 I)	I 2	4	2	2	100	1		0	0	1	100	
	II 5	4		3	75	5		0	0	1	20	
	III 3	2		2	100	3		1	33			
HAWKES (1901 II)	I 2	2		2	100	1		0	0	1	100	
	II 2	4		4	100	1		0	0	1	100	
	III 2	2		2	100	0		..	..	..	..	
HEINSBERGER II	I 2	3		2	67	1		0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †v/g	Affected		No.	X or †v/g	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
LAEBER 1902-GUZMAN 1913	III 2	8	4	4	50	6	2	2	50	1	1	i
BRAMWELL (1903)	I 2	3		1	33	2		0	0	2	100	
	II 2	3		1	33	2		0	0	..	..	
	II 3	2		1	50	5		0	0			
KOWALEWSKI (1906)	II 2	3		2	67	1		1	100			j
USHER (1906)	II 3	8		3	38	3		3	0			
	III 7	3		2	67							
CONTO (1907)	I 1	3		2	67	1		0	0	1	100	
	I 3	2		1	50							
	II 3	1		1	100	1		0	0			
HANCOCK (1908)	II 1	3		3	100	5		0	0	5	100	
	II 6	3		1	33	1		0	0	..	..	
	III 2	4		0	0	5		0	0	1	20	
	IV 1	1		1	100	0		..	..	..	..	
	III 3	4		1	25	2		0	0	..	..	
	III 4	3		3	100	4		0	0	0	0	
NETTLESHIP (1909, IV)	I 1	6		4	67	2		0	0	1	50	
	II 7	1		1	100	2		0	0	..	..	
(1909, VI)	I 4	4		2	50	1		0	0	..	..	
(1909, VII)	I 2	6		4	67	2	1	0	0	..	..	
EVANS (1909)	I 3	6	2	3	75	3	1	0	0	1	50	
	II 9	4	1	1	25	0		0	0	..	..	
BACH (1909)	III 4	1	0	1	100	0						
RAYMOND & KÖNIG (1909)	II 1	3	0	1	33	2		0	0	2	100	
	III 1	2	0	1	50	1		0	0	..	..	
	III 2	1	0	1	100	0		..	..	..	..	
MUGGE (1911, II)		3		2	67	0		..	..	..	..	k
LUTZ (1911)	III 2	5		3	60							
	II 7	2	1	1	100	2	1	0	0	..	..	
	II 3	2		2	100	2		0	..	1	50	

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †yg	Affected		No.	X or †yg	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
TAYLOR & HOLMAN (1913 II)	0	3		1	33	4	1	0	0	2	67	
	I 2	6		4	67	4				0	0	
	I 5	3		3	100	4				1	33	
HENSON (1917 II)	I 1	2		1	50	3	0	0	0	2	67	
	II 3	0				2	0	0	0	2	100	
	II 5	0		..	..	4				2	50	
	III 1	2		0	100	0	0	0	0	..	..	
	III 2	3		1	33	0	0	..	..	..	..	
	III 7	2		1	50	3	0	0	0	..	..	
	III 9	2		1	50	1	0	0	0	..	..	
FLEISCHER & JOSENHAUS (1920)	I 2	2		1	50	3	0	0	0	3	100	
	II 3	4		0	0	2	0	0	0	1	50	
	II 4	3		2	67	3	0	0	0	2	67	
	III 4	2		2	100	4	0	0	0	3	75	
	III 10	3		0	0	3	0	0	0	1	25	
	III 15	3		2	67	2	0	0	0	1	50	
	IV 1	6		3	50	1	0	0	0	..	..	
	IV 2	5		2	40	6	0	0	0	..	..	
	IV 3	1		1	100	1	0	0	0	..	..	
	IV 16	4		2	50	0	..	..	..	..		
	IV 21	1		0	0	1	0	0	0	..	..	
	IV 27	5		1	20	3	0	0	0	..	..	
DULEUTRA (1920) ERO	II 7	3		2	67	2	0	0	0	..	..	
MORLET, (1921) ERO	I 2	7	1	5	84	4	0	0	0	3	75	
	II 2	6	2	3	75	6	1	1	20	..	..	
	II 4	1	0	1	100	4	0	0	0	..	..	
	II 9	6	?	2	33	1	0	0	0	..	..	

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †yg	affected		No.	X or †yg	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
VOGT & (KNÜSEL) 1922	II 1	2	0	2	100							
	II 2	3	1	2	67	4	1	0	0	3	100	
	III 7	4	1	1	33	6	1	0	0	..	..	
GINZBURG (1923)	II 8	2		1	50	2		2	100	..	..	1
HIRSCH (1923)	III 11	2		2	100	3		0	0	3	100	
	IV 25	2		1	50	1		0	0			
	IV 28	1		1	100	2		0	0	..	..	
WORTON (1913)	II 1	4		2	50	4		0	0	1	25	
	II 2	2		1	50	3		0	0	1	33	
	III 2	7		3	43	1		0	0	0	0	
WAARDENBURG (1924)	II 1	2		1	50	3		0	0	3	100	
	III 1	3		2	67	3	1	0	0	0	0	
	III 2	3		2	67	4		1	25	4	100	
	III 4	5		2	40	3		0	0	3	100	
	IV 7	3		1	33	0		0	0			
	IV 8	1		1	100	1		0	0			
	IV 9	1		1	100	1		0	0			
	IV 16	4		2	50	4		1	25	..	..	
	IV 20	2		1	50	0		..		..	..	
	IV 23	6		1	17	1		0	0	..	..	
MEYER-RIEMSLOH (1925)	IV 4	3	2	1	100	9	2	1	14	6	100	
	V 4	3		3	100	3		0	0	2	67	
	V 9	0	..	..	..	2	..	0	0	2	100	
	V 12	1		0	0	2		0	0	1	50	
	VI 4	3		2	67	3		0	0	2	67	
	VI 15	1		1	100	1		0	0	1	100	
	VI 16	1		1	100	0		..	..	..	..	
	VI 17	3		3	100	0		0	0			

TABLE 2a (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †♂	Affected		No	X or †♂	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
MEYER-RIEMSLOH (1925)	VI 19	1		0	0	3		1	33	..	..	
	VI 20	2		2	100	7	1	0	0	1	16	
	VI 22	4		1	25	0	..	..	..	..	..	
KROPP (1927)	II 4	3		2	67	3		0	0	..	..	
USHER (1927)	III 1	3		1	33	4		0	0	..	..	
	III 3	2		1	50	3		0	0	..	..	
	III 7	2		1	50	7		0	0	..	..	
	III 32	2		1	50	2		0	0			
	III 34	3		1	30							
	III 35	1		1	100							
USHER (1927a)	III 10	4		3	75	6		0	0	..	..	
KAWAKAMI (1926)	III 5	3		1	33	5		2	40	..	..	
	II 4	1		1	100	1		0	0	..	..	
	II 7	2		1	50	0		..	..	..	..	
	III 19	4		2	50	3		1	33	..	..	
	III 26	3		2	67	5		2	40	..	..	
Grand Total		444	25	263		345	17	26				

a. LEBER (1871) found daughter unaffected. SCHILLING (1875) found daughter affected but gives no ophthalmoscopic findings (DREXEL 1922, p. 54)
b. NETTLESHIP, 1909 p. clxii, figure 87. DREXEL 1922, p. 107.
c. The daughter has atropic colored papillæ; narrow vessels.
d. Other sibs?
e. Atrophic opticus.
f. Two other children, sex unknown.
g. DREXEL expresses doubt if typical Leber's disease; 3 cousins show white papillæ.
h. Not all children of III 3 certainly known.
i. Other daughters affected left side, a central color section, papillæ red gray. Not typical ♀; one daughter shows absolute central scotom; also temporal half papilla white.
j. Daughter shows central scotom and opticus atrophy.
k. Mother's mother's brother affected.
l. One of 2 daughters examined ophthalmoscopically.

TABLE 2b

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating II, F, normal; M, affected.

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or *tyg*	Affected		No.	X or *tyg*	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
HASWELL (1888)	II 2	7		6	86	2		..	..	2	100	a
SYM (1891)	I 2	3		3	100	2		0	0	2	100	b
BACH (1909)	II 2	3		3	100	1		0	0	1	100	
WAARDENBURG (1924)	IV 14	2		1	50							
MEYER-RIERISLOH (1925)	V 8	3	1	2	100	4	2	0	0	..	..	
IRONSIDE (1926)	II 1	2	..	2	100	3	..	0	0	..	..	
USHER (1927)	III 22	0		..		1	..	0	0			
KAWAKAMI (1926)	II 11	2		0	0	2		0	0	1	50	
	II 12	2		1	50	4		2	50	2	50	
	III 30	1		0	0	3		0	0	0	0	
	III 31	2		1	50	4		2	50	..	..	
Grand Total		27		19		26		4				

a. No special age data in unaffected son; did he die before age of onset of disease.

b. Mother affected at 51 years (after menopause).

TABLE 2c

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating III. Father affected; M. genoytpically N.

REFERENCES	SONS					DAUGHTERS				CONDUCTORS		Remarks
	Reference to Mother	No.	X or †yg	Affected		No.	X or †yg	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
HASWELL (1888)	III 1					2		0	0	..	..	a
	III 5											b
	III 9											c
	III 10											d
	III 11											e
	II 3											f
TAYLOR	IV 1	1		0	0	2		0	0	..	..	
GOULD (1893)	III 1											g
	V 5	0				1		0	0	..	..	
	V 9	4		0	0	2	..	0	0	..	..	
	V 23	0		0	0	2		0	0	..	..	
WESTHOFF (1895)	II 4	4		0	0	0	1	0	0	..	..	
	II 5	1		0	0	3		0	0	0	0	
RAYMOND (1898)	II 2	2		0	0	0	..	..	..	..	..	
HORMUTH (1900)	II 1	2		2	100	..	..	..	..	..	..	
BRAMWELL (1903)	II 1	1		0	0	3		0	0			
USHER (1906)	III 12	2		0	0	2		0	0			h
COSTE (1907)	II 4	1		0	0	1		0	0			
HANCOCK (1908)	I 1	3		0	0	3		0	0	2	67	i
	III 5	3		0	0	3		0	0			
	III 8	1		0	0							
	III 1	4		0	0	3		0	0			
EVANS (1909)	I 1	0				1		0	0			
	I 7	1		0	0	0		..	..	..	..	
	II 7	1		0	0	1		0	0			
RAYMOND AND KÖNIG	II 2	2		0	0							
TAYLOR AND HOLMES (1913 II)	II 15	2		0	0	2	1	0	0	..	..	
	II 2	5	2	0	0	1	0	0	0	..	..	
FLEISCHER AND JOSENHAUS	IV 6	4	0	0	0	0	0	0	0	..	..	

TABLE 2c (*continued*)

REFERENCES	Reference to Mother	SONS				DAUGHTERS				CONDUCTORS		Remarks
		No.	X or †*vg*	Affected		No.	X or †*vg*	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
VOGT AND KNÜSEL (1922)	III 3	0	..	..	..	1	..	0	0	..	..	
	III 5	2	..	0	0	0	..	..	..	..	..	
GINSBERG (1923)	III 7	3	0	3	100	0	..	..	..	..	..	j
HIRSCH (1923)	III 7	2		0	0	4		0	0	..	..	
	III 8	1		0	0	2		0	0			
	III 10	2		0	0	2		0	0			
	IV 25	1		0	0	2		0	0			
WORTON (1913)	III 12	4		0	0	1		0	0	..	..	
	III 15	4		0	0	..		0	0	..	..	
WAARDENBURG (1924, I)	IV 3	0		..	..	2		0	0	..	..	
	IV 21	1		0	0	5		0	0			
MEYER-RIEMSLOH (1925)	VI 3	1		0	0	0	..	..	..	..	..	
	VI 10	0	..	..	..	2	..	0	0	..	..	
	VI 11	0	..	..	..	2	..	0	0	..	..	
IRONSIDE (1926)	II 2	4	..	0	0	6	..	0	0	..	..	
KROPP (1927)	II 1	2		0	0	3		2	67	..	..	k
USHER (1927, II)	III 4	6		0	0	4		0	0			
	III 8	1		0	0	1		0	0	..	..	
	IV 92	2		0	0	1		0	0	..	..	
	III 56	5		0	0	1		0	0	..	..	
USHER (1929, I)	II 5	1		1	0	1		0	0	0	0	
	III 17	2		0	0	2		0	0	0	0	l
Grand Total		39		5		41		2				

a. Also 4, sex unknown N.
b. 5, N, sex unknown.
c. 4, N, sex unknown.
d. 3, N, sex unknown.
e. 5, N, sex unknown.
f. 7, N, sex unknown.
g. 14 children, all N.
h. Also some additional daughters, unaffected.
i. The father (I 1) showed onset at 25 and later recovery, like grandsons!
j. Father and all 3 sons examined ophthalmoscopically, whitened papillæ.
k. "Diagnose von Lebersche familie Optikus atrophie nicht absolut sicher."
l. No grandchildren or other descendants affected.

TABLE 2d

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating IV. F, affected; M, conductor.

REFERENCES	REFERENCE TO MOTHER	SONS				DAUGHTERS				
		No.	X or †♀♀	Affected		No.	X or †♀♀	Affected		Conductor
				No.	Percent			No.	Percent	
KAWAKAMI 1926	II 9	3		2	67	1		0	0	
Total		3		2		1		0		

TABLE 2e

Incidence of hereditary opticus atrophy in progeny of specified matings. Mating V. F, affected; M, affected.

REFERENCES		SONS				DAUGHTERS				CONDUCTORS		Remarks
	Reference to Mother	No.	X or †♀♀	Affected		No.	X or †♀♀	Affected		No.	Percent of fertile females	
				No.	Percent			No.	Percent			
WAARDENBURG (1924)	V 26	3		1	33	3		0	0	0	0	a
USHER (1927)	III 6	0				0						
Total		3		1		0		0				

a. Children mostly under 21; daughters probably under 15 years.