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The Problem of Complete Y-Linkage in Man[1]

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THE FIRST CHROMOSOME IN MAN which was identified as the carrier of specific genes was the X chromosome (Wilson 1911). The second and, at present, the only other identifiable chromosome for which such a status has been claimed is the Y chromosome.

Inheritance through the Y chromosome, Y-linkage, may occur in two ways, complete and incomplete. In complete Y-linkage a gene responsible for a certain trait is solely confined to a locus in the Y chromosome either because it has no allele in the X chromosome or because it does not exchange with an X chromosomal allele. In incomplete Y-linkage, or more correctly, incomplete sex linkage, there are homologous loci in the X and Y chromosomes whose alleles cross over from one sex chromosome to the other. In organisms with heterogamy of the male sex, complete Y-linkage of genes with full penetrance leads to the following phenomena:

a) The trait occurs in males only.

b) It reoccurs in all sons of affected males.

c) The daughters of affected men are not only phenotypically normal but also do not have affected offspring.

Incompletely sex linked genes behave differently from completely X- or Y-linked genes. In complete X-linkage a gene is located in a portion of the X chromosome which does not undergo exchanges with the Y chromosome. Such genes follow the classical distribution of the X chromosomes. In particular, a heterogametic XY parent transmits his X-linked genes exclusively to his XX offspring. Conversely, in complete Y-linkage, the XY parent gives his Y-linked genes exclusively to his XY offspring. In incomplete sex-linkage both XX and XY offspring may inherit a specific allele of the gene concerned, in frequencies which depend on the amount of crossing over between the homologous regions of the X and Y chromosomes.

It was not until 1920 that the Y chromosome in any species was shown to be concerned with the transmission of a particular gene. In that year Johannes Schmidt demonstrated the role of the Y chromosome in the genetics of a pigment spot in the fish *Lebistes reticulatus*, a discovery which, in 1921, was also reported by Aida for color inheritance in the fish, *Aplocheilus latipes*. In the following years, a few more cases of Y-linked inheritance became known; further examples in *Lebistes* (Winge 1922a, b)[2]; a color trait in the beetle *Phytodecta variabilis* (Zulueta 1925); bristle size in *Drosophila*

[1] The material of this paper formed the basis for the Presidential Address "On porcupine skin and hairy ears; or, The alleged sins of the Y chromosome" delivered at the tenth annual meeting of the American Society of Human Genetics at the University of Michigan, Ann Arbor, Michigan, April 13, 1957.

[2] For references to later works on Lebistes by various authors, see Winge and Ditlevsen 1938.

(Stern 1926, 1927); and the only Y-linkages in plants, concerned with general morphological abnormality and with chlorophyll variegation respectively, in *Melandrium album* and *M. rubrum* (Winge 1931). In *Drosophila*, the Y chromosome is also known to influence the degree of position effect variegation (Gowen and Gay, 1933, 1934) and to cause variegation of eye color if present in double dose in normal females, or triple dose in normal males (Cooper 1956). Other examples of special morphological expressions of the Y chromosome in *Drosophila* have been given by L. V. Morgan (1947), and Goldschmidt, Hannah, and Piternick (1951). Action of Y chromosomes on quantitative characters of *Drosophila* has been reported by Mather (1944), Barrigozzi (1948), and Barrigozzi and di Pasquale (1953). For a review of much of the work on the Y chromosome of *Drosophila* and additional literature see Hannah (1951).

The Y chromosome is concerned with sex determination in the fishes mentioned above, the gypsy moth *Lymantria dispar* (see Goldschmidt 1934), the silk worm *Bombyx mori* (Tazima 1943, 1944 quoted from Goldschmidt 1955), the mosquito *Culex molestus* (Gilchrist and Haldane 1947), several species of the midge *Chironomus* (Beerman 1955) and the plant *Melandrium* (Warmke and Blakeslee 1939, Warmke 1946, Ono 1940 a and b, Westergaard 1940, 1948).

In *Drosophila* the Y chromosome is not involved in sex determination in the strict sense, since animals without a Y chromosome but one X chromosome are males (Bridges 1916) and animals with one or two Y chromosomes but two X chromosomes are females (Bridges 1916, Stern 1929). However, spermatogenesis in XO males does not lead to motile sperm and thus results in sterility (Bridges 1916, Shen 1932, Schultz 1947). In mammals the possible role of the Y chromosome in sex determination or male fertility is unknown. As in *Drosophila* the Y chromosome is without influence on sex in the plant *Rumex acetosa* (Ono 1935).

The existence of Y-linked inheritance in man was first suggested by Castle (1922) and Enriques (1922), after Schofield (1921) had described a pedigree of unusual inheritance of webbed toes. Castle, referring to the then recently published work on Y-linkage in fishes, pointed out that "Schofield's article furnishes evidence that the Y chromosome type of inheritance occurs in man as well. . ." Gates, in his book *Heredity and Eugenics* (1923), accepted this explanation. The revised edition, published under the title *Heredity in Man* (1929) mentions the Y chromosome in connection with webbed toes as wells as other pedigrees of human abnormalities. Haldane (1932) referred in passing to Y-linked inheritance of webbed toes, the skin abnormality of the Lambert family of "porcupine men", and "very probably" certain types of hypospadias. A more detailed treatment was given by Cockayne (1933) who listed Schofield's webbed toe pedigree under the section-heading "Sex-linked Y-chromosome Inheritance (Holandric)"[3] and stated that he knew "of only three other pedigrees which are most easily explained by assuming the presence of a dominant gene in the Y-chromosome." These three included the Lambert family, families with a skin defect called keratoma dissipatum and a family with hypertrichosis of the ears.

Incomplete sex-linkage in *Aplocheilus*, based on crossing-over between homologous

[3] The term holandric was coined by Enriques (1922) to describe a type of inheritance in which all males are affected and in which females neither exhibit the trait nor transmit the underlying gene. The only example in any organism known to Enriques was that of the Schofield family.

segments of the X and Y chromosomes, had been discovered by Aida (1921) and was soon found in some other animals. Haldane, in 1936, reported on the results of "A search for incomplete sex-linkage in man". The paper has stimulated much further work but the existence of this type of inheritance in man has increasingly become doubtful (Morton 1957). The present review will only be concerned with pedigrees which seemed to permit an interpretation in terms of complete Y-linkage. For the sake of simplicity the adjective "complete" will usually be omitted.

When, in 1946, Gates published his compendium on Human Genetics—invaluable as a source book, in spite of errors which few could have avoided in a task this size—he listed 14 traits under the heading "Genes in the Y." (p. 82-83). These were the following, in Gates' wording with a running number added as well as a reference to the page on which they will be considered below:

1. Ichthyosis hystrix (p. 161)
2. Black hairs in the ears (p. 158)
3. Webbed toes (p. 158)
4. Coloboma iridis (?). Sedgwick's case (p. 151)
5. Cataract (?). Harman's case (p. 154)
6. Keratoma dissipatum (3 fams.) (p. 156)
7. Peroneal atrophy, 1 case of cross-over, X—Y (p. 151)
8. Epidermolysis bullosa simplex (Yaffe) (p. 152)
9. Radio-ulnar synostosis (1 ped.) (p. 152)
10. Hyperextensibility of thumbs? (1 ped.) (p. 154)
11. Hypermobility of joints (1 ped.) ? (p. 154)
12. Blue sclera and brittle bones (1 ped.) (p. 154)
13. Adherent tongue (possible) (p. 155)
14. Camptodactyly (1 ped.)? (p. 153)

For a few other traits the possibility of Y-linkage is mentioned later in the text but apparently none seemed sufficiently likely candidates for this category to be included in the foregoing catalogue. It is seen that the 14 traits listed include one in which "1 case of cross-over X — Y" is noted. Otherwise the intent of the table would seem to have been a listing of only completely Y-linked genes since it does not contain any of the genes considered as partially sex-linked at that time. Most of the 14 traits listed in 1946 do not appear any more in Gates' (1954) summary of human linkage data. The only ones left are those numbered 1, 2, 3, and 9 above with a new one added:

15. "(probably) foot ulcers" (p. 155)

The most recent tabulation of Y-linkage in man, in the *Handbook of Biological Data* (1956) consists of items 1, 2, 3, and 6 plus:

16. "Color vision anomaly" (p. 162)

The following survey will be concerned with all sixteen traits though at different length. An additional trait:

17. "Abnormality of the external ear" (p. 163)

will also be included. Hypospadia will not be considered. Sörensen (1953) provides evidence that genes for these male-limited abnormalities are transmitted by both sexes.

CRITERIA FOR ABSOLUTE Y-LINKAGE

In its simplest form absolute Y-linkage results in all sons and none of the daughters of an affected male being affected. Two main kinds of exceptions from this expectation can be envisaged due to (a) incomplete penetrance and (b) non-disjunction of the sex chromosomes. With incomplete penetrance some sons may appear to be not affected while all daughters would obey the basic expectation that they are not affected. With non-disjunction, zygotes with one X chromosome but without a Y chromosome (XO) and others with two X chromosomes plus a Y chromosome (XXY) could be formed. In Drosophila XO individuals are males and XXY individuals females. Obviously such exceptional males do not inherit the Y-linked gene from their father while the exceptional females do. In man, it is not known whether XO and XXY zygotes would develop into males and females, respectively. If they do, exceptions from typical Y-linkage could be expected.

As will be seen later, all traits suspected as being based on Y-linked genes are so rare that only very small numbers of relevant individuals have been recorded. When, in these pedigrees, deviations from Y-linkage are encountered they may be taken rather as raising doubts as to the existence of this type of inheritance than as legitimate exceptions from it. Non-disjunction is a rare process whose occurrence may be looked for in large collections of data only. Its apparent presence in one or a few out of a very limited total of families should immediately suggest a search for some other explanation than Y-linkage.

Incomplete penetrance is a frequent phenomenon. If it occurred in the manifestation of a Y-linked gene it would tend to obscure the existence of its localization in the Y-chromosome. Instead of only affected sons from affected fathers non-affected sons would appear, in proportions depending on the frequency of penetrance. Such sibships would simulate segregation for a dominant autosomal gene. The daughters, of course, would remain uniformly non-affected but, with small data, the possibility would be considerable that autosomal segregation would, by chance, not have caused the production of affected females.

Even if the data do not offer any exception from expectation for complete Y-linkage other types of explanations must be explored. A simple possibility is that an autosomal dominant gene is responsible for the trait under discussion and that the observed presence of the trait in all males and its absence in all females is nothing but the result of chance. Another possibility is that the trait is again due to an autosomal dominant gene but that its expression is limited to the male sex. In this case one would still have to assume that its presence in all males of a given sibship is the product of chance but the absence of its expression in females would be the expected result of its sex limitation. While half of the male progeny of half of the females should of course be affected by the expression of a dominant autosomal gene carried by the mothers the number of such progeny-tested females would have to be considerable to be of sufficient bearing on the alternative Y-linkage or autosomal inheritance in case of absence of affected sons.

In Y-linkage the probability of obtaining only affected males and neither affected nor transmitting females is 1. In contrast, the probability of such a finding in autosomal dominance with or without sex limitation will always be smaller than 1. This,

however, does not mean that it is a more likely hypothesis to assume Y-linkage than either one of the two other types of inheritance. The *a priori* probability of finding a gene in the Y chromosome is small. Not only is the Y chromosome one out of 23 (or more) chromosomes of the set, and not only is it one of the smallest chromosomes, but all evidence from mammalian genetics speaks against it being a frequent carrier of completely Y-linked genes. No such gene would have likely been overlooked but none has been discovered in the extensive experimental work with mice, rats, guinea pigs, rabbits, cats, dogs, and other experimental or domesticated animals.[4]

It is hardly possible to assign a quantitative value to the *a priori* probability of finding a Y-linked gene in man, but it may well be of the order of the probability of finding a segregation for a dominant autosomal gene which among 10 or 12 individuals appears to be distributed to all males and to no females.

Finally, there is the problem of selective recording of holandric pedigrees. If the trait concerned is frequently encountered in pedigrees with an autosomal dominant type of inheritance special emphasis may be placed on an occasional holandric appearing kindred. Even a family some of whose members exhibit a unique trait may have a higher probability of being made the subject of a publication if all males of one or more sibships are affected and no females than if there were no apparent correlation of the trait with sex.

ANALYSIS OF 17 PRESUMABLY OR POSSIBLY Y-LINKED TRAITS

The seventeen cases whose inheritance has been ascribed to a completely Y-linked gene carry individually different weight. In some there is evidence at the onset against Y-linkage. In others, the possibility of Y-linkage deserves more careful consideration. The cases with *prima facie* evidence against Y-linkage will be discussed first.

Coloboma iridis

A single pedigree, reported by Streatfield (1858) after Sedgewick (1861), contains six bilaterally and one unilaterally affected male, in three generations. One male sib of affected persons is normal as are four female sibs of affected males. The only one of these females who was recorded as having had offspring was the mother of three affected sons. This is clearly not a case of Y-linkage.

Peroneal atrophy

In an extensive pedigree of peroneal atrophy (Herringham 1889, after Gates 1946) with otherwise typical complete recessive X-linked inheritance there was one sibship of two with an affected son and a carrier daughter. The father was affected. "This case of direct transmission from father to son could be explained by crossing-over between the X and the Y chromosomes so that one of the father's germ cells carried the gene in the Y." (Gates 1946 p. 967). Whether this or another explanation is valid, complete Y-linkage is excluded.

[4] Eichwald and Silmser (1956) have described a more rapid rejection by female recipients of skin grafts from male than from female donors of inbred strains of mice, a difference which conceivably could be attributed to a specific affect of the Y chromosome. Fox (1956) has rightly pointed out that this is not the only likely explanation.

Epydermolysis bullosa simplex

Yaffe's extensive pedigree (Yaffe 1942) contained originally 13 affected males descended in three generations in the male line from an affected man (Fig. 1). No normal male sibs were present. All seven female sibs were unaffected, but there was no information on their offspring, if any. This seemed to constitute one of the strongest cases for Y-linkage. Fortunately, the history of the family was followed up by Gates. In a footnote, he reports (1946; p. 299) that "correspondence elicits the further information that the normal sister (III-9) of four affected brothers had three normal daughters and an affected son. Hence the gene crossed over from the Y to the X chromosome."

The disease is usually caused by a dominant autosomal gene with not fully complete penetrance. Yaffe's kindred may have been a selected case of this type with the "improbable" sex distribution of the trait being due to chance. Complete Y-linkage is ruled out by the information quoted.

Radio-ulnar synostosis

Davenport, Taylor and Nelson (1924), presented a large pedigree of four generations with bilateral radio-ulnar synostosis occurring in three generations with 12 affected males and 12 not affected female sibs. One affected man had, in addition to two affected sons, also an affected daughter and a non-affected son. Gates (1946) comments that "this sibship can be explained on the assumption of crossing-over

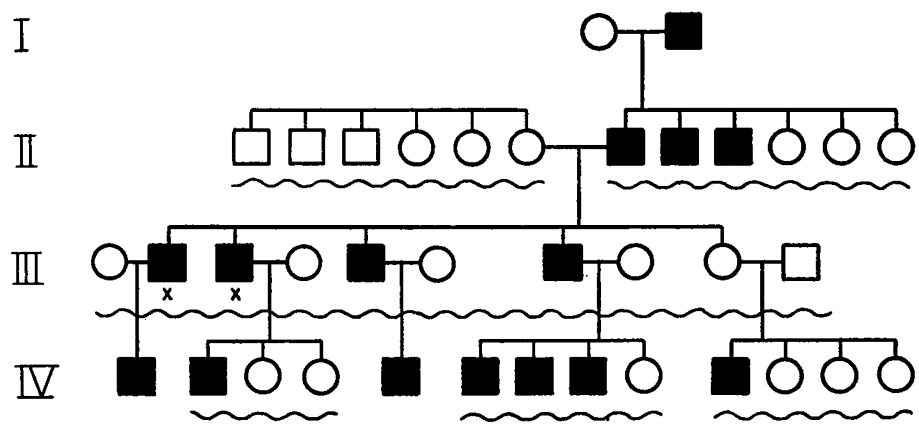

FIG. 1. EPIDERMOLYSIS BULLOSA. AFTER YAFFE AND GATES (1946).

Symbols used in this and later figures:
↗ propositus
X individuals seen by the investigator
∿∿ sequence within sibship not stated.
Numbers within enlarged male or female symbols indicate number of such individuals.
Numbers below symbols indicate ages.
This and the following pedigrees either have been redrawn from those given by the original investigators and usually include some additional information, or have been constructed from their statements.

from Y to X . . ." In any case, the presence of an affected daughter removes the trait from the category of complete Y-linkage.

Camptodactyly

Fantham's pedigree (1924) begins with an affected man and his normal wife and contains 10 affected males and 12 non-affected females in four generations descended in the male line from the initial couple (Fig. 2). No offspring is recorded for any of the females and there were five normal male sibs of the 10 affected males. One of the normal males had two sons and two daughters, all normal.

The trait, bent little finger, was incompletely penetrant within the same individual, being manifest on the left hand only (in *all* affected individuals?). Given such intra-individual incomplete penetrance it may be assumed that some of the normal individuals also carried the genetic basis of camptodactyly which remained unexpressed on both hands. An autosomal dominant with absence of affected females either due to chance segregation or non-penetrance appears a more likely explanation than Y-linkage.

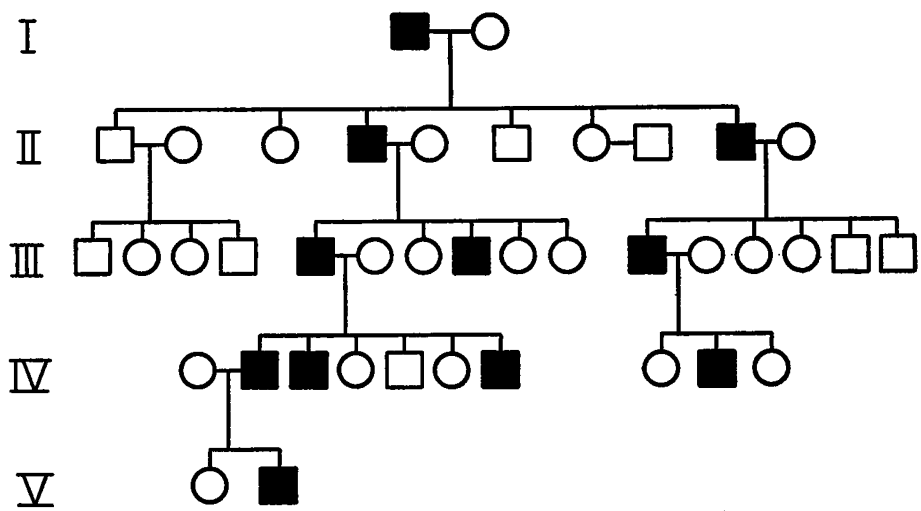

FIG. 2. CAMPTODACTYLY. AFTER FANTHAM.

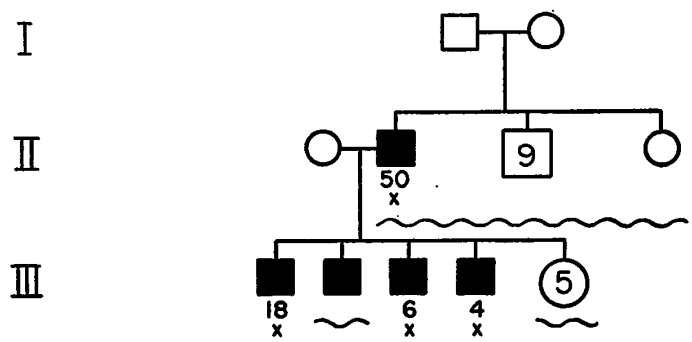

FIG. 3. HYPERMOBILITY OF JOINTS. AFTER KEY.

Hyperextensibility of thumbs; Hypermobility of joints; Blue sclera and brittle bones

Under the heading "Hypermobility of joints as a sex linked hereditary characteristic" Key (1927) described a family tree of three generations (Fig. 3). Beginning with a normal couple, the second generation consisted of nine normal males and one normal female plus one male who showed hypermobility of joints. This man had five normal daughters and four sons all of whom had hypermobility and bilateral clubfoot of two different types. One aspect of the "hypermobility of joints" is "hyperextensibility of thumbs". Gates (1946) deals with the same family under both headings, in different chapters (pages 797 and 448). Evidently by some error, (Key mentions that abnormal mobility of the joints is a feature in brittle bones and blue sclera) the family is described a third time by Gates as having contained the syndrome "brittle bones, blue sclera and hypermobility of the joints" (p. 767). This earned it a third listing among Y-linkage under the heading "blue sclera and brittle bones". The "three" suspected cases of Y-linkage thus were really a single one.

The genetics of clubfoot is complex. It often has been considered as due to a recessive gene, with incomplete penetrance, but also as due to a dominant, with incomplete penetrance. Clubfoot occurs about twice as frequently in males as in females. Key's case may be regarded as that of a syndrome in which clubfoot and hypermobility are different aspects of the same underlying defect. The affected father of the sibship of nine may be considered as a *forme fruste* in which clubfoot remained unexpressed. Perhaps he was heterozygous for an incompletely dominant gene for clubfoot and hypermobility which he transmitted to his four sons but either did not transmit to his five daughters or transmitted to some daughters where it was not penetrant. Since no offspring of any of the daughters is recorded, further light cannot be thrown on this question. As it stands, the family hardly contributes to the consideration of complete Y-linkage.

Cataract

In 1846, G. S. Dyer published a report under the title "Case of cataract in both eyes; occurrence of the Affection in the Males of three Generations" (see also Harman 1910). In reality, the pedigree (Fig. 4) shows three successive sibships II, III,

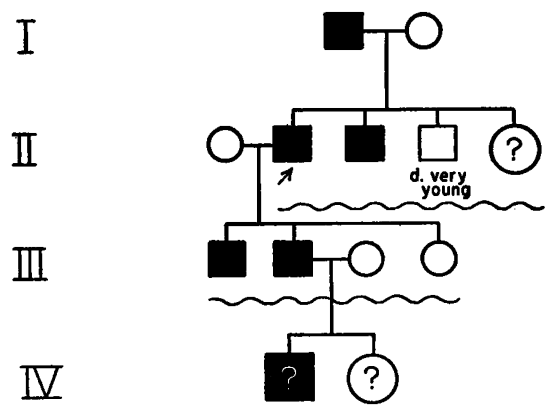

FIG. 4. CATARACT. AFTER DYER.

and IV containing affected males who are descended from an affected man in generation I. All males were affected (omitting one who died very young) and all females were normal. Apart from the first recorded male there are two affected males in II, two more in III, and an unspecified number of affected sons in the "large family" which forms the final sibship IV. There were "several" daughters in sibship II, one in sibship III and an unspecified number of daughters in the "large family" IV. One may conclude that there were more than six affected males and more than six normal females—probably considerably more of both types. No offspring of any of the females is noted. Cataract is normally inherited as a simple autosomal dominant and very many pedigrees have been recorded. It seems wisest not to single out one pedigree in which by chance ordinary autosomal transmission may have led to the appearance of holandry.

Adherent tongue

According to Weiss (1929) whose father, a professor of orthodontics, provided him with the information, a young man with a speech defect was observed who was not able to "elevate the tongue to make contact with the palate". The propositus reported that he had three brothers all of whom had a speech defect (one slight, one medium, and one severe) and four normal sisters (Fig. 5). His father also had a medium speech defect. The father had three brothers, one affected about the same as himself, and two very severely affected, and four normal sisters. A reference to an affected uncle fails to make it clear whether this was one of the father's brothers or another individual. Omitting this male there were eight males with speech defects and eight normal females, a much more significant distribution than that of four affected males and four normal females given by Gates (1946) who omits the sibs of the father (apart from the "uncle"). No offspring of the females is recorded. The pedigree is suggestive of Y-linkage but the trait involved is an unreliable one. The term "adherent tongue" is not founded on an anatomical diagnosis and it is not known whether a limited mobility of the tongue was the cause of the speech defects of any of the persons other than the propositus. The variable degree of the defect among the males raises the question of possible sex limitation or sex control so that females would not manifest it or do so more rarely even if the genetic basis were present. Again, little weight can be assigned to this trait in its bearing on Y-linkage.

Foot ulcers

A family with some members affected by neurotrophic osseous atrophy leading to ulcerations of the soles of the feet was described by E. M. Smith (1934; Fig. 6.)

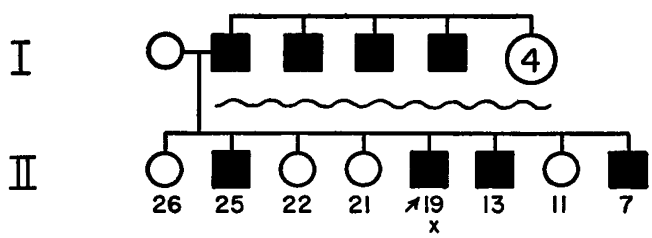

FIG. 5. ADHERENT TONGUE. AFTER WEISS.

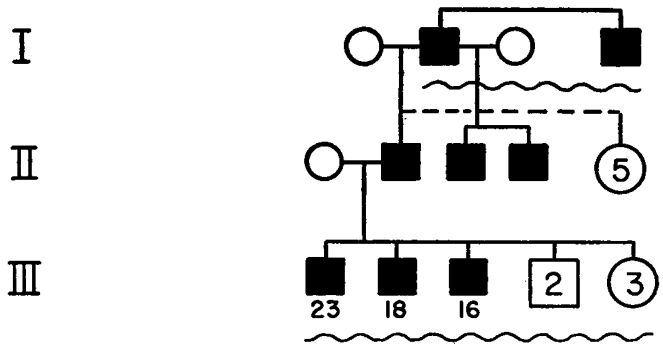

FIG. 6. FOOT ULCERS. AFTER E. M. SMITH. IT IS NOT KNOWN HOW THE FIVE FEMALES OF II WERE DISTRIBUTED OVER THE TWO MARRIAGES OF I-2.

Eight males were known to have been affected in three generations and five female sibs of the affected males in generation II were normal. In the last generation there were three affected males as well as two normal brothers and three normal daughters.

Unfortunately, the age or birth order of the sibs in generation III was not given. The defect develops only during the second decade of life. If the two normal brothers (and their three sisters) were too young to have shown the defect they can be disregarded, but if they were old enough their normal condition would not be compatible with Y-linkage. Dr. Elmer Maurice Smith died in 1946, so that no information additional to that published could be obtained.

The pedigree offers the same problems as several others in this series. It fits Y-linkage (if the five normal sibs of generation III are disregarded) but can also be considered a case of extreme deviation from the transmission of an ordinary autosomal dominant. Sex-limitation is not excluded since no information is available on offspring of the normal women in generation II.

Keratoma dissipatum

This skin defect is one of the four traits which Cockayne recognized as Y-linked. Gates (1946) reported on three families with the defect, the first one described by Brauer (1913), the second by Junghanns (1922) and a third whose source is not given. The detailed account of the "third" family makes it certain that it is none other than that of Brauer's which thus has been used twice.

The published information on Junghanns' family is given in a report on a meeting of a regional German dermatological association. Translated into English the part containing Junghanns' contribution reads as follows:

> "Junghanns: Keratoma hereditarium dissipatum palmare et plaetare (sic) (Brauer) in a 53 year old man which began in his 20th year and remained stationary in the last years. Inheritance in the male members of the family in the third generation."

Clearly, no conclusion can be drawn from such limited data.

This leaves only the first family for serious consideration. The original pedigree comprises four generations (Fig. 7). Since, however, all members of the last generation were too young to have developed the lesions even if they possessed the defective

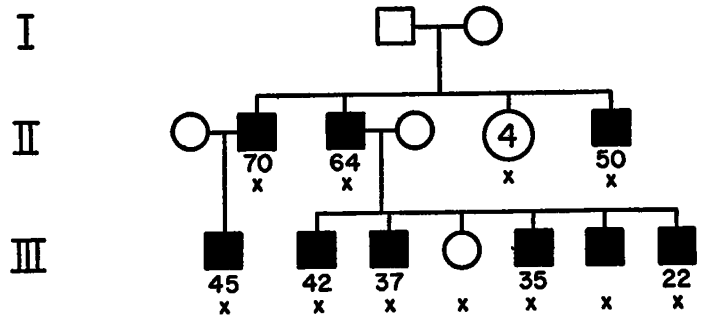

FIG. 7. KERATOMA DISSIPATUM. AFTER BRAUER. GENERATION IV HAS BEEN OMMITED SINCE ALL INDIVIDUALS WERE TOO YOUNG TO HAVE BEEN ABLE TO SHOW THE CONDITION.

genotype, they do not contribute to the understanding of the inheritance. The first generation (I) consisted of two normal parents. They had seven children (II), three affected sons and four normal daughters. Two of the sons had jointly six affected sons and one normal daughter (III); the third son left no offspring. The four normal daughters of generation II had, altogether, eight sons and four daughters, all normal (III).

This is an interesting pedigree not only because all nine males of generations II and III were affected and all females not affected but also because it seems to be a case where one of the parents of generation I was a genetic mosaic. Since both parents were somatically normal but produced three sons each of whom have received a mutant abnormal gene, part or all of the gonads of one parent must have carried the mutant. This situation makes it impossible to state whether the four females of generation II were normal because the keratoma gene never is transmitted to females, or whether only germ cells from a non-mutant gonad or a non-mutant sector participated in their conception.

The case would be weakest as an indicator for complete Y-linkage if the four females of generation II were omitted from consideration. In this case the relevant individuals would be the total of nine affected males and the one normal sister in the six children sibship of generation III.

The case would be strongest in favor of the interpretation of Y-linkage if it were assumed that all seven sibs of generation II came from a mutant region of the gonads of the mosaic parent. In this case there would be 14 relevant sibs in two generations consisting of nine affected males and 5 normal females. If an autosomal dominant gene were involved the probability of this sex distribution would be very small.

A skin defect, keratoma maculosa, which depends on an autosomal dominant gene is known from fourteen families (Cockayne 1933). Keratoma dissipatum is clinically and histologically indistinguishable from keratoma maculosa. Why then has it been separated from this more frequent condition and given a special name? The only reason is the holandric heredity of the trait in the Brauer family. This seems to be a paradigm of selective recording in human genetics. The probability of finding a pedigree with a holandric sex distribution of a trait must be viewed in relation to the total number of pedigrees of the trait. If one, or two, pedigrees, with holandric

distribution are placed into a separate category then they appear to be unique. If they are considered together with many other pedigrees their apparent uniqueness can be viewed as an extreme deviation from a sex-independent distribution.

These arguments are not decisive in an absolute sense. They leave open the alternative: autosomal dominant versus Y-linked gene. But they remove keratoma dissipatum from its relatively secure position in the list of Y-linked genes.

Hypertrichosis of the ears

Tommasi's (1907a, b) pedigree of a family in which all ten male descendents in the male line from an affected male ancestor and none of the seven female descendents had ears whose rims and surfaces were strikingly covered with long hairs has, since Cockayne called attention to it, seemed to represent rather strong evidence for complete Y-linkage (Fig. 8A). A reading of the original descriptions raises considerable doubts. Minor doubts arise in connection with the individuals of the last generation (V). There were two not affected brothers (not twins as in the pedigree constructed by Gates, 1946). This normality is not significant since the boys were too young to show the condition. However, it opens the question how many of the four females in generation V had reached an age in which they would have shown the hairiness provided it could appear in women. There are no data on record and the birth order of the sibs is also unknown. Graver doubts relate to the reliability of the pedigree as a whole. The propositus, III-6 and his wife III-7, were the only individuals personally seen by Tommasi and all information on the other members of the five generation pedigree comes from them. But III-6 was 81 years old when questioned and an inmate of a mental institution. It was at least the fourth time that he had been hospitalized for periods of four or more months at a time, for such conditions as alcoholism, psychomotor excitement, and religious delirium, at the ages of 42, 52, 55, and 81 years. His parents and other close relatives were also alcoholics and mentally abnormal. It may well be asked how much confidence can be based on such sources of information.

Gates (1957) has recently observed in Indians several new cases of similar hypertrichosis as that of Tommasi's patient. Gates also points out that the trait has been described in some other Italian individuals. It may be a not-too-rare characteristic. All affected individuals were males and in four cases more than one man occurred in a sibship or in successive generations (Fig. 8B–E). The data are fragmentary and no offspring from normal female sibs of affected males have been recorded. There is no evidence against complete Y-linkage of the characteristic and further studies should be attempted. On the other hand, hypertrichosis of the ears may be suspected to be male sex-limited, independent of Y-linkage. It may well be in the same class as growth of hair in the external auditory meatus of older men, or the growth of the beard. In this case, one would expect unaffected women to transmit the trait. Until evidence is available on this question judgement may well be postponed.

Webbed toes

Schofield's (1921) pedigree (Fig. 9) of webbed toes in his own family shows 13 affected male descendents in the male lines from an affected man (I-2), 11 not af-

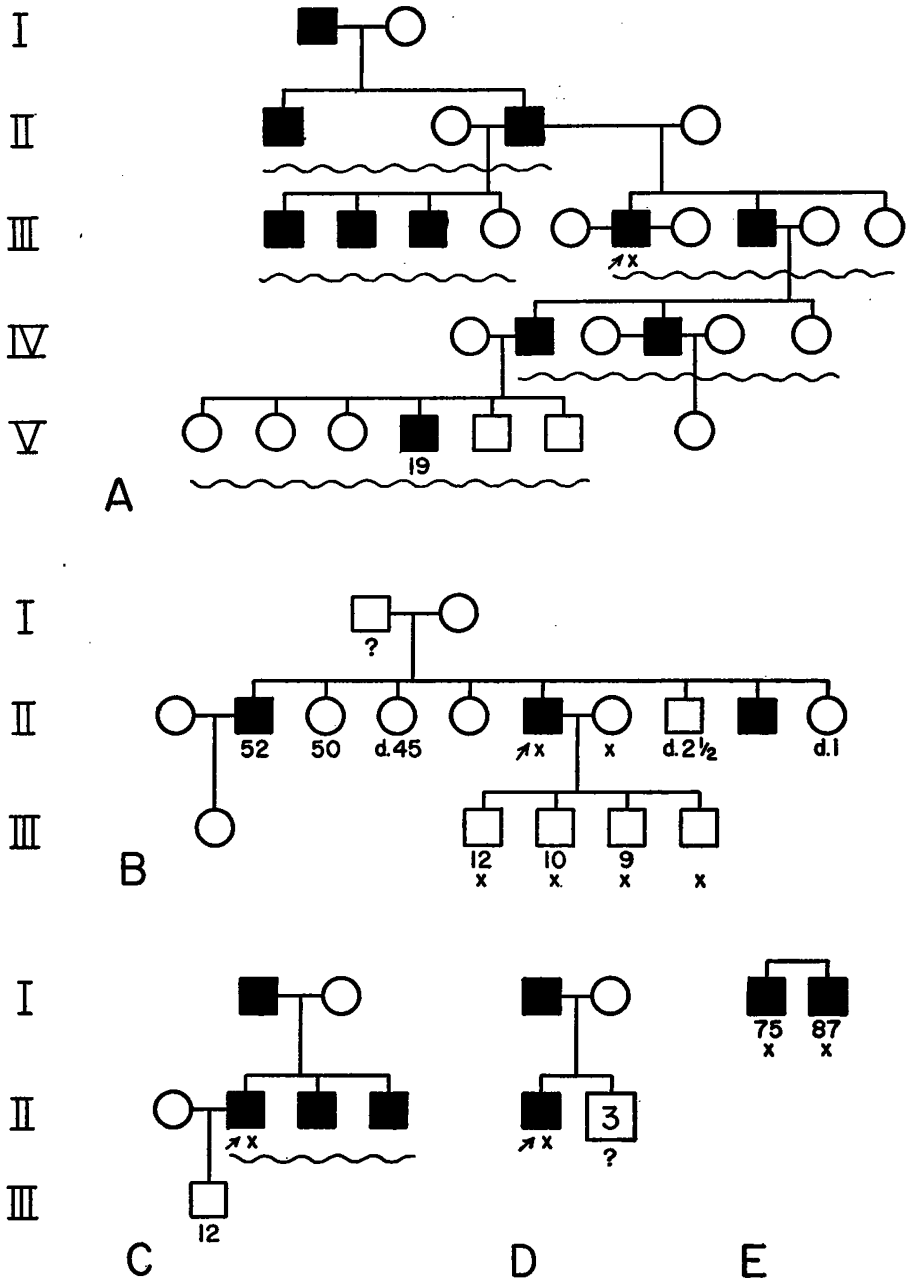

FIG. 8. HYPERTRICHOSIS OF EARS.

A. AFTER TOMMASI. V-5 AND V-6 EITHER WERE YOUNGER THAN V-4 OR DIED BEFORE AGE 19.
B-D. AFTER GATES (1957).
E. AFTER CAINER (1898).

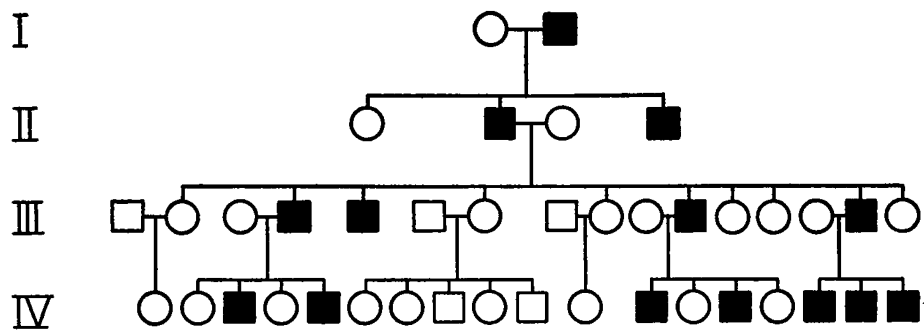

FIG. 9. WEBBED TOES. AFTER SCHOFIELD.

fected female sibs of affected brothers and a total of two normal sons and five normal daughters in the progeny of three not affected female sibs of generation III. By itself the pedigree not only is fully in accord with an interpretation in terms of complete Y-linkage but deviates widely from the random sex distribution of affected persons to be expected from an autosomal dominant. Yet, there are reasons for hesitation.

The original publication was extremely brief. No details were given regarding the sources of information for the designations "affected" and "not affected". The degree of webbing was described as variable and two outline drawings of feet accompanied the article but it remained obscure whether the decision webbed or not webbed was always clear-cut or whether borderline cases were encountered.

Enriques, in 1924, concluded a critical discussion of Schofield's note with the following paragraph:

> "At any rate, Mr. Schofield has caused us to be somewhat embarrassed with this single pedigree, so small and so strange. Since he tells us that just in his family he has seen such traits, there is nothing left for us but to respectfully urge him and all members of his family, male and female, to produce many children, many male children and many female children, for the love of science. Then in twenty or thirty years, the Lord willing, we shall be able to ascertain the importance of this point on the theory of heredity."

Attempts by the writer of the present review, who then was unaware of Enriques' suggestion, to visit Dr. R. Schofield and to obtain addresses of a few members of the family were politely discouraged (exchanges of letters in 1948, 1956). Thus, the opportunity has been denied for restudy of some of the individuals in this important pedigree of 1921, and to investigate additional members of the family. All those who have been born in the intervening decades have shown, according to Schofield (letter to the writer, 1948), as far as his knowledge went, the same characteristic lines of inheritance as in the original family material.

Webbing of toes is known from extensive other pedigrees and usually follows the transmission of an autosomal dominant gene. Penetrance is frequently incomplete and rarer in the female than the male sex. On the basis of these facts Gates expresses the opinion that an autosomal dominant may be involved in all cases, including that of the Schofield family. An unpublished study of Professor F. E. Stephens from Utah, kindly made available to the author, is particularly relevant to this interpretation. In a large kindred webbed toes seemed at first to be typically holandric in distribu-

tion. Further search, however, uncovered some non-affected males and one affected female. The manifestation of webbing apparently was mostly suppressed in the female sex and the surplus of affected over non-affected males was a chance phenomenon.

It is regrettable that the first human trait which has been regarded as due to a completely Y-linked gene must at present remain in the group of undecided cases.

Ichthyosis hystrix

The "porcupine men" of the English Lambert family have been famous ever since the first one was presented before the Royal Society in 1731. Cockayne, in 1933, compiled a pedigree in which twelve affected males are entered in six consecutive generations together with seven not-affected female sibs (Fig. 10A). An intensive restudy of the original literature and a search of the parish registers of births, christenings, marriages and burials has led to a radical re-evaluation of the evidence for holandric inheritance of the porcupine trait (Penrose and Stern, in preparation). It has become clear (Fig. 10B) (a) that the only affected individuals for whom reliable records exist were four males, in generations II, III, and IV; (b) that there were two females and three males among the five sibs of III-2; (c) that the sibship of generation IV consisted of at least six instead of two males, one probably unaffected, and probably only one instead of seven females; and (d) that the two affected males of

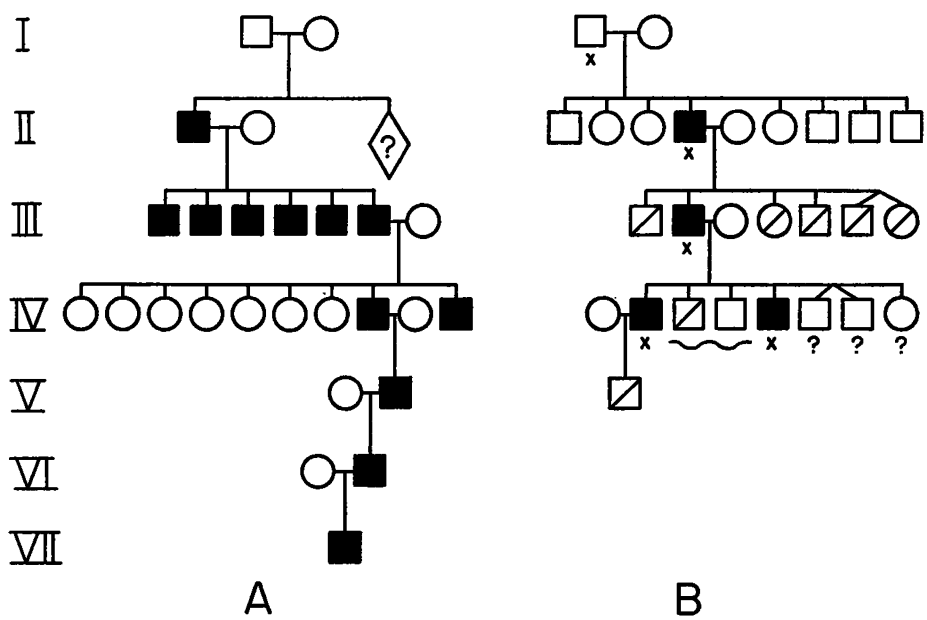

FIG. 10. ICHTHYOSIS HYSTRIX, THE LAMBERT FAMILY.

A. AFTER COCKAYNE.

B. AFTER PENROSE AND STERN. SYMBOLS WITH AN OBLIQUE LINE INDICATE THAT THESE INDIVIDUALS WERE REPORTED TO HAVE BEEN AFFECTED. THE WAVY LINE IN IV INDICATES THAT THE SEQUENCE OF IV-3 AND IV-4 AMONG THEMSELVES IS UNKNOWN. THE ZYGOSITY OF THE TWINS IN IV IS UNKNOWN. THE QUESTION MARKS SIGNIFY ABSENCE OF INFORMATION CONCERNING TRAIT.

generations V and VI have actually never been recorded and had been entered in the pedigree due to misreading of earlier accounts. If the recorded statements of II-1 that *all* his children had been affected are accepted then the fact that two of them were girls eliminates further consideration of Y-linkage. If, on the other hand, only individuals are considered who were seen by competent students then all that is left are four affected males. Only a selective elimination of the two females III-4 and III-7 and of the male IV-4, but a retention of other equally unascertainable members of the family would decrease again the probability for inheritance of an autosomal dominant but certainly not enough to re-establish the case for Y-linkage.

A similar though less spectacular family group of ichthosis hystrix has recently been investigated by Curth and Macklin (1954). Here females as well as males were affected though clearly much milder than the males. It is possible that the Lambert family carried a similar autosomal dominant gene as the one in this family.

Color vision anomaly

S. C. Reed, Cambier and Applen (1951) have given a short report on the family of the second of the three authors, in which an anomaly of color vision is stated to have been present in all ten males descended in the male line from an affected man and have been absent in all five female descendents in the male lines (Fig. 11). None of the total of five sons and four daughters of four of these five females were affected (the fifth woman remained childless). "Unfortunately it has not been possible to test the members of the family in a satisfactory manner." (Reed, et al.). The anomaloscope could not be used and at most five of the men were given pseudoisochromatic plate tests which showed them to be deficient. The authors themselves seem confident of the written or verbal statements of the members of the family "which were very definite. Each person was quite certain as to his or her possession, or lack, of a color vision anomaly." Yet the authors themselves begin their discussion of the inheritance with the careful phrase "If the evidence presented by the members of this family is accurate . . ."

If it is, then the authors calculate that the probability is negligible that the color vision anomaly of the Cambier family is of the usual X-linked type. (There is, of

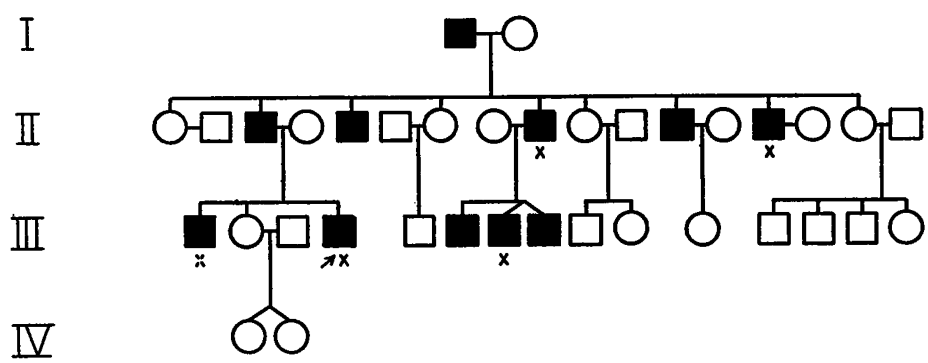

FIG. 11. COLOR VISION ANOMALY. AFTER REED, CAMBIER AND APPLEN. THE ZYGOSITY OF THE TWINS IN III AND IV IS UNKNOWN. THE TYPE OF COLOR TEST GIVEN TO III-1 IS NOT KNOWN.

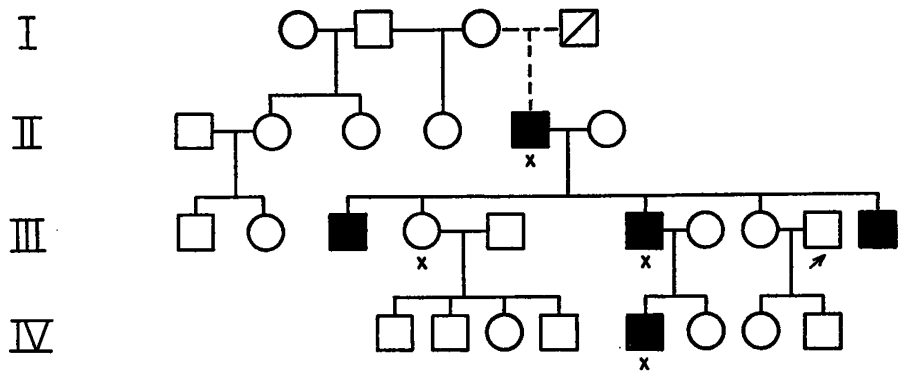

FIG. 12. ABNORMALITY OF THE EXTERNAL EAR. AFTER CROW (UNPUBLISHED). THE PATERNITY OF II-5 FROM I-4 IS CONJECTURAL. I-4 IS SAID TO HAVE BEEN AFFECTED.

course, insufficient information available as to the type of color defect present.) They also reject a hypothesis involving crossing over of a normally X-linked gene to the Y chromosome. They assume that the gene for color vision deficiency in the family represents a mutation in the non-homologous section of the Y chromosome.

There is no discussion of the possibility that an autosomal dominant gene may be involved. Such a gene may have been the basis of the color vision defect in the famous Cunier family (Stern and Walls, 1957). If really all evidence presented is to be accepted then the probability in favor of the reported sex distribution of the trait being due to chance segregation of an autosomal dominant is very small though much larger than that calculated for a recessive X-linked trait. One should hesitate, however, to base any definite conclusion on a pedigree which involves the type and amount of uncertainty as the one under discussion.

Abnormality of the external ear

Professor J. F. Crow has kindly made available for discussion here a pedigree involving an abnormality of the pinna, so that the external ear is greatly reduced in size and appears almost shell-like (Fig. 12). According to Crow's informant, a graduate student of the University of Wisconsin, the expressivity is quite variable though all individuals have clearly deviant external ears. Some have also a mild facial paralysis and one person had an unilaterally abnormal middle or inner ear.

The paternity of II-5 from I-4 is a matter of presumption based on an interpretation of some family tradition. The pedigree fits expectations from Y-linkage but, with rather low probabilities, also conforms to extreme segregations based on either an ordinary autosomal dominant or a male sex limited autosomal dominant. "My feeling about this is that it is a pedigree suggestive of Y-chromosome inheritance, but of course not conclusive." (letter from J. F. Crow, November 28, 1956).

CONCLUSIONS

The evidence for Y-linkage in man is at best ambiguous. The "best" pedigrees, taken by themselves, have only a low probability of being interpretable as the result of chance segregation of autosomal genes but such an interpretation becomes more

acceptable if one realizes that these pedigrees have been selected from thousands showing ordinary autosomal or X-linked inheritance. It is significant that, with the exception of hypertrichosis of the ears, each case of supposed Y-linkage is represented by a single family group. If there were really normal alleles in the Y chromosome of normal individuals then one might expect mutations to abnormal alleles to occur sufficiently frequently to be discovered in more than single pedigrees.

A decision not to accept any one of the known conditions as due to proven Y-linkage should, however, not be equivalent to a neglect to search for new evidence. One or another of the traits discussed may still turn out to be truly Y-linked. There may exist in the Y chromosome some normal genes with a very low mutation rate, or, as Haldane (1936) pointed out, the Y chromosome may occasionally receive, by translocation, genic material with morphologic expression from another chromosome. That the Y chromosome has a function of its own is attested by its very existence. What it is still must be discovered.

SUMMARY

An analysis of the evidence concerning sixteen traits formerly regarded as possibly or presumably being due to completely Y-linked genes and a new trait of similar inheritance leads to the conclusion that some pedigrees must definitely be excluded from complete Y-linkage. All others may be accounted for by assuming unusual sex distribution of an autosomal dominant gene due to chance or in addition by assuming sex limitation. For a few pedigrees the probabilities of the last assumptions are small and a final decision must await further data.

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