GENETICAL EVIDENCE FOR A CYTOLOGICAL ABNORMALITY IN MAN.

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Chromosomal abnormalities are very common, not only in plants, but in such well-studied animals as *Drosophila melanogaster*. In this fly, even if high non-disjunction lines are neglected, aberrations are very frequent, certainly more so than any particular mutation, possibly more so than all mutations. For example, primary non-disjunction both of the X and of the fourth chromosome occurs about once in 2000 individuals. The aberrant types produced by the former event persist for many generations. We might therefore expect cytological abnormality to be reasonably frequent in man.

In this paper *prima facie* evidence is brought forward that certain women are of the constitution $\widehat{XX}Y$, the two X-chromosomes being attached, so that they pass into the same gamete. Such individuals show abnormal genetical properties in two ways, as they do in *Drosophila*. In the first place if such a woman has a sex-linked recessive gene in each of the attached chromosomes (represented by X's in Fig. 1) she will hand

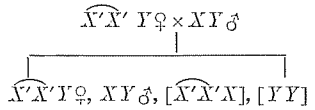

Fig. 1.

down the sex-linked recessive character to all her daughters and none of her sons, provided that the $\widehat{X'X'}X$ zygotes are inviable, as they generally are in *Drosophila*. If any survive, they may be expected to be abnormal in many respects, like the *Drosophila* super-females. They would probably display the dominant character, but might not do so if two recessive genes predominate over one dominant. YY zygotes are certainly inviable. Thus such women should hand on a character which is usually a sex-linked recessive, in the female line.

If an $\widehat{XX}Y$ woman with a normal chromosome pair marries an $X'Y$ man, carrying a sex-linked recessive, he should hand this character on to all his sons and none of his daughters (Fig. 2). Now this might also happen because the mother was heterozygous for the gene concerned. In such a case the expectation is that half the sons and daughters should be

affected with the recessive character. But in a small family it might well be handed to all the sons and none of the daughters. Hence in a large number of pedigrees of colour-blindness, for which women are commonly heterozygous, we should expect to find a few cases of this kind. Evidence for the existence of $\widehat{XXY}$ women must be sought for in pedigrees of rare sex-linked abnormalities, where it is extremely unlikely that an affected man would marry a heterozygous woman, unless she were related through his mother.

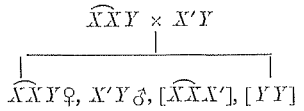

Fig. 2.

A cursory search through the literature reveals six pedigrees illustrating transmission in the female line. These are summarised in Table I. In each case the women are related in the direct female line, and all daughters of affected women who have reached the age of incidence are themselves affected. No sons of any affected women are affected. The number of unaffected sons is given. Unfortunately all the pedigrees are incomplete, and I have been unable to trace the original reference to Cunier's pedigree of ichthyosis. Colour-blindness, haemophilia, and ichthyosis are well known as ordinary sex-linked recessives. Sedgwick's pedigree of blind-

TABLE I.

Character	No. of affected women	No. of unaffected sons	Reference
Colour-blindness	13	6	Cunier (1839)
Haemophilia	4	0	Enriquez (1922)
,,	3+1?	1	,,
Amaurosis	4	?	Sedgwick (1863)
Ichthyosis	13	?	Cunier, *fide* Gates (1929)
Cataract	7*	14	Enriquez (1922)

* Besides these one woman reached the age of 65 without developing cataract, which occurred in the remainder at about 50. She may or may not have been a real exception.

ness dates from a period before ophthalmoscopy had been developed. The age of incidence varied from thirteen to thirty-five years. The condition may therefore have been Leber's disease, or possibly retinitis pigmentosa, both of which are occasionally sex-linked recessives. The pedigree of cataract refers to senile cataract, and is not entirely convincing, since many members had not reached the age of incidence. I do not know of any pedigree in which senile cataract is transmitted as a sex-linked recessive. But the fact that in five out of six cases the con-

dition is commonly inherited as a sex-linked recessive is extremely striking. There can be little doubt that Enriquez was correct in supposing that the *X*-chromosome was somehow concerned in the phenomenon, which he calls diagynic heredity.

Two alternative explanations may be considered. We may be dealing with a plasmon, or extra-nuclear factor, such as is common in plants. But no clear case of such a factor is known in animals, and the coincidence that the diseases are normally sex linked remains unexplained. We should also have to make the further assumption that the action of the plasmon was limited to the female sex. Or we may be dealing with a dominant gene, sex limited in its incidence. Unfortunately no data exist as to the daughters of the unaffected sons of the affected women. But the probability that all the twelve female descendants of the original affected woman in Cunier's case should be affected is 1 in 4096 on this hypothesis, so it need not be seriously considered. Hypotheses can also be framed involving selective fertilisation, but until the phenomenon has been demonstrated elsewhere in animals they need not detain us.

Nettleship (1908), in his pedigrees of night-blindness, usually transmitted as a sex-linked recessive, records four cases where the condition was transmitted by a father to one or more sons. In the first case (Fig. 166) the wife was a cousin on the mother's side, and possibly heterozygous; in the other three (Figs. 174 and 178) no consanguinity is recorded. In the latter three cases the children were:

One affected son;

Two affected sons and six unaffected daughters;

Two affected and one unaffected sons, two unaffected daughters.

On our hypothesis the unaffected son could be explained by the coming apart of the two attached *X*-chromosomes, which sometimes occurs in *Drosophila*. The probability of obtaining a distribution as irregular or more irregular on the basis of maternal heterozygosity is 1 in 1024, and Nettleship's results therefore support the hypothesis here developed.

A possible objection to the hypothesis is that females containing a *Y*-chromosome might be expected to be abnormal in some respect. For though they are normal in *Drosophila* the human *Y*-chromosome does not seem to be quite as empty of genes as that of the fly. Enriquez has called attention to holandric inheritance, *i.e.* the handing on of a character from a man to all his sons and none of his daughters or their descendants. Such characters include webbed toes, the skin abnormality of the Lambert family of "porcupine men," and very probably certain

types of hypospadias. If the latter is due to abnormality in a gene carried by the Y and responsible for normal development of the male genitalia, we might expect a certain amount of abnormality in $\widehat{XX}Y$ females. This may well have escaped detection, even if it occurs.

If $\widehat{XX}Y$ women exist, it is likely that XXY women are still commoner. Such women would occasionally form XX and Y gametes, but usually X and XY. Thus a sex-linked recessive man marrying such a woman would generally produce normal offspring, but occasionally transmit his defect to a son. It would be extremely difficult to detect XXY women by genetical means.

Finally a case may be mentioned which could be explained by trisomy of an autosome. This is Haselhorst and Lauer's (1930) case where a mother belonging to group AB, and married to a group O husband, produced a child belonging to group O. The group membership of mother and child was confirmed by a number of investigators, and its injury at birth precluded the possibility of a mistake. Hence either an A or B gene had mutated to O, or some other anomaly had occurred. Thus the mother may be a mosaic due to dispermy, or she may contain three of the chromosomes carrying the blood group genes. In favour of the latter hypothesis it must be remembered that trisomy of 1 out of 24 chromosomes might be expected to have less somatic effect than trisomy of the small fourth chromosome in *Drosophila*.

In order to prove or disprove the hypothesis of this paper two things are needed. In the first place more pedigree material of the same type should be collected. In the second, a technique for the counting of human chromosomes without involving the death of the person concerned is greatly to be desired. It seems possible that satisfactory mitoses might be observed in a culture of leucocytes. If so, the development of human cytology in relation to genetics will become possible.

SUMMARY.

Evidence is adduced from pedigrees that certain women are of constitution $\widehat{XX}Y$, the two X-chromosomes being attached.

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