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Chromosomes and Natural Selection

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1. Introduction

Gene mutations can be lethal in their effects, they can be mildly disruptive and diminish individual fitness, they can be neutral or even slightly favourable. The same is true for chromosomal aberrations. Consequently, natural selection in populations can be set up by alterations in chromosomal structure just as it is by gene changes which affect the hereditary material of a species. There are, however, important differences in the manner by which selective effects are produced following the various kinds of spontaneous change.

The present paper deals primarily with chromosomal changes but there are two ways in which selection may act on them. First, there is the immediate effect of an aberration upon the fitness of an individual who carries it and which leads to persistence or extinction of that particular aberration. Secondly, there is the less direct effect of an aberration upon the frequency of any gene which may be responsible for inducing it. Study of the immediate effects is comparable to the analysis of the behaviour of mutant genes in populations by classical methods (Fisher 1930, Wright 1931, Haldane 1932). Study of the second, less direct, process is comparable to the analysis of the behaviour of mutagenic genes (mutators).

2. Chromosomal Aberrations and Fitness

The main types of aberration, which have to be considered, are (a) non-disjunction, (b) deletion, fusion and translocation, as well as (c) internal rearrangement, especially inversion; non-disjunction (a) implies alteration in chromosome number whereas the other changes, (b) and (c), imply chromosomal breakage. Many examples are now known in man which are covered by these headings.

(a) Non-disjunction

The result of non-disjunction is often lethal or severe enough to prevent transmission of the aneuploid state. In mongolism this is evident since perhaps only one case in a hundred thousand has offspring so that, for practical purposes, the fitness is zero. The same probably applies to the YXX and other variants of aneuploidy in the Klinefelter syndrome. Turner's

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syndrome, with single X and no Y, has a very low fertility rate. Evidence from examining other clinical types associated with non-disjunction points in the same direction, especially trisomy of No. 13 and No. 17. However, the example of mongolism shows that, in the rare case in which the defect is transmitted to the next generation by secondary non-disjunction, the superficial appearance is like classical dominant inheritance (Hanhart 1960). So that unless non-disjunction caused unfitness, the aberrant karyotype would increase in the population with its continuing spontaneous recurrence. In fact, the frequencies of these aberrations are determined by balance between the degree of unfitness of the aneuploid type and the natural rate of primary non-disjunction. A puzzling example, nevertheless, is that of the triple X female, where fitness is not grossly diminished but in which transmission by secondary non-disjunction must be rare, if it occurs at all. Here the frequency of the condition seems to depend upon three factors, the individual fitness, the rate of spontaneous non-disjunction and the viability of abnormal gametes.

(b) Translocation

Over twenty years ago, the effects of balanced translocation in a parent upon the offspring were demonstrated in mice (Snell, Bodemann & Hollander 1934). A balanced parent could produce unbalanced gametes and, consequently, deformed offspring with too much or too little chromatin. It seemed likely that the same kind of process might occur not uncommonly in man (Haldane 1938, Penrose 1939). Now there is direct evidence of this. Examples of centric fusion with probable loss of an inessential fragment have been found repeatedly in those cases of mongolism where maternal age is not an aetiological factor. The fused chromosomes which have been formed by translocation can be transmitted for three or four generations. From time to time a kind of secondary non-disjunction produces unbalanced gametes which lead to zygotes with too much chromatin, effectively trisomic or partially trisomic. Several other translocations have been seen in man and in the balanced state they can be transmitted through normal parents. Large translocations affecting chromosomes Nos 2, 4 or 6 are easily identified (Fraccaro 1961, Edwards 1961) but there may be a multitude of smaller ones waiting to be detected.

It seems not improbable that the human race may be polymorphic for several balanced translocations. If so, some interesting consequences should be examined. To be heterozygous for a balanced translocation is disadvantageous in so far as there is a risk of producing unbalanced gametes and the term " semisterile " has been used for normal carriers of translocations. However, in the homozygous state, balanced translocations would present no such disadvantage and would be as fit as homozygotes with normal karyotype. In a population containing both, random mating would be consistent only with one point of equilibrium of the unstable type at the translocation frequency of 50 per cent, comparable with the gene frequency expected when the heterozygote is unfit (Haldane 1941). In circumstances of close inbreeding, however, or strongly assortative mating, there exists the possibility of stable equilibrium because two populations of homozygotes can maintain themselves independently. Indeed very intense consanguinity can quickly establish families of true breeding homozygotes with advantage over hybrid matings. The population will gradually separate into two groups whose numbers

will depend only upon their relative initial sizes. It remains to be seen whether we shall find small separate human populations with all members homozygous for special balanced translocations.

(c) Inversions

Somewhat similar considerations about selection apply both to balanced translocations and inversions. Evidence for the presence of inversions in man, however, is, as yet, slight. Suggestions of suppression of crossing over in some pedigrees and changes in satellite formations point to the likelihood of inversions in certain families. The association of malformed offspring with unusually large satellites in a parent has been reported several times but the mechanism is obscure. If the large satellite represents an inverted segment, this might, after crossing over in that segment, cause abnormal gametes to be formed with acentric or dicentric chromosomes. It is also possible that presence of an inversion could interfere with pairing at meiosis and induce non-disjunction.

The question of natural selection and inversions has special interest because of observations on *Drosophila* populations (Dobzhansky 1946). Some hybrids, heterozygous for inversions, have been found to be noticeably more fertile than members of the parent stocks. If inversions which occurred in man carried similar properties, the increased fitness conferred could balance any damage occasionally produced in gametogenesis and such inversions would persist in the population.

3. Genes which induce Non-disjunction

Primary non-disjunction is believed to arise usually from unpredictable accidents but genetical analysis shows that definite causes must be considered. In so far as trisomy of No. 21, No. 17 and X are concerned there is definite evidence that advancing maternal age is significant. For Klinefelter's syndrome the effect is less and for Turner's it is hardly detectable. In the only deeply analysed example, mongolism, it seems clear that about one quarter of the cases have causes unrelated to maternal age. In Klinefelter's syndrome the proportion is much larger (Penrose 1961). Among the 25 per cent of age-independent mongols, about 5 per cent can be accounted for by translocation. The rest may have quite different causation. In view of the occasional occurrence of more than one kind of trisomy in the same family or in the same person, the suggestion can reasonably be made that in man, as in *Drosophila*, there are genes which disturb meiotic pairing (Sturtevant 1929). The typical pattern is defective oogenesis, but not defective spermatogenesis, in homozygotes.

To trace genes of this sort in man would be difficult but there is one obvious test, namely, the search for parental consanguinity in mothers of trisomics. In a sample of over 600 cases of mongolism which I have compiled during some thirty years, I have consistently enquired about consanguinity in grandparents. I found only 3 with father and mother related. There were, however, 5 with the father's parents related to one another (a normal frequency) and 10 with the mother's parents related. The patients with consanguineous maternal grandparents also had lower maternal ages than the general average for mongols.

This result is suggestive but not convincing evidence for the existence of maternal recessive predisposition to autosomal non-disjunction. If such a predisposing gene exists it cannot be very rare. It may be worth while to ask how would selection act for or against its perpetuation? Homozygotes will have reduced fitness because a proportion of their offspring will fail to reproduce. Stable equilibrium would be attained if the implied loss of genes in each generation were offset by mutation. The rate would be measured by half the incidence of sterile offspring. So far as mongols are concerned, if 20 per cent of them were caused in this way, the mutation rate of the gene would have to be rather high, e. g. 1/6000. There might, however, be compensating advantages for heterozygous mothers by way of increased fertility. It is conceivable that these heterozygous mothers may still be liable to produce unbalanced gametes but only at late maternal ages. There is some evidence that these mothers belong to a group in chich the child-bearing period is prolonged. According to calculations made on existing data, one mother in 20 could be a heterozygote of this type. This would mean that normal extra offspring would be born at late ages and would overcompensate for the few abnormal offspring. Stable equilibrium could thus be obtained for a gene which caused mongolism without presupposing any mutations.

4. Miscellaneous Questions

There remain for discussion a few important miscellaneous questions; for example, chromosomal mosaicism. In most cases this condition must arise by mitotic non-disjunction in the early stages of individual development. Rarely it may be the result of incorporation of tissues from a twin. Mitotic non-disjunction could arise accidentally or because of the presence of a " sticky " gene like that found in maize (Beadle 1932) which interferes with both meiosis and mitosis in homozygotes. A rare gene of this type in man would be indicated if parental consanguinity had a raised incidence for mosaic aneuploids. In mosaicism the unfavourable effectes of aneuploidy for the individual tend to be alleviated in so far as the proportion of normal cells present is large; but the possibility of transmission of the aberration remains so long as a few germ cells are aneuploid. Some maternal age-independent mongols are the results of mosaicism in unaffected parents. In such circumstances the ultimate origin of the anomaly in the patient could, again, be a recessive trait in the parent.

Another phenomenon is triploidy, presumably initiated by an unreduced gamete fertilizing a normal one. Since the second meiotic division of the ovum is a late occurrence in maturation, the mother, again, is more likely than the father to be causally implicated. The origin of mosaic triploid-diploids in man (Böök & Santesson 1961) and in lower animals remains obscure. The general question of selection acting upon gametes which is involved here has not been fully discussed. Experimentally differential selection in sperms has been shown for the T-locus in the mouse (Dunn 1960). In mongolism there is clear indication of selection against unbalanced sperms because of the rarity of paternal transmission and absence of paternal age relationship. The exception is in the case of translocations involving two small acrocentrics (Fraccaro, Kaijser & Lindsten 1960) where paternal transmission occurs.

Finally, there is an extensive range of phenomena which should enter into a discussion of this if enough facts were known. These concern the relation of viruses to genes. It is easy to imagine that episomal nuclear material (Jacob & Wollman 1961) attached to chromosomes

may be present in cells and persist for generations, behaving in many respects like genes, inducing aberrations. Another property of such particles when free from the chromosomes can be to induce tumours. In human pedigrees such processes can be investigated by searching for malignancy in relation to aneuploidy. At present very little can be said about the significance of such associations in connection with selective forces but, in this field, researches in human genetics are likely to provide some important clues in the near future.

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