RECENT ADVANCES

IN

HUMAN GENETICS

Edited by

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M.A., M.D., F.R.S.,
Galton Professor of Eugenics, University College, London

With the assistance of
HELEN LANG BROWN

With Illustrations

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PREFACE

THE study of heredity in man, after a long and comparatively quiet period of incubation, has erupted violently during the last decade into a most exciting and productive activity. This development has been made possible by the application of a variety of special techniques which include such diverse methods as statistical devices for the detection and measurement of linkage, paper chromatography and electrophoresis of body fluids and the use of colchicine and hypotonic solutions to make chromosomes clearly visible in cell cultures. It is impossible to provide the student with an equally complete account of new work in all fields so that certain aspects have been selected here for detailed presentation and others almost entirely neglected. There should be enough advances reported in the present volume to whet the reader's appetite for descriptions of other parts of the subject elsewhere. The largest omission is concerned with human biochemical genetics but this subject has been recently very adequately covered in well-known treatises such as that of H. Harris. The gap is compensated by information from other branches.

Knowledge of chromosomes has been presented here fully by D. G. Harnden. Problems of the genetics of sex are explained by O. J. Miller. Biochemistry, in one of its most significant genetical aspects, is dealt with by P. S. Gerald in his chapter on hæmoglobins. Some new work on quantitative genetics, exemplified by the analysis of finger prints, is described by Sarah B. Holt. The mathematically minded reader is also catered for by the chapter by J. H. Renwick about the order of genes on chromosomes and that by C. A. B. Smith on the uses of modern methods of statistical analysis. For the more general reader there are accounts of mutation and malformations which, it is hoped, will be useful.

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April 1960.

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CHAPTER 1

MUTATION

by

L. S. PENROSE

THE term mutation was first introduced by de Vries (1901) to signify a discontinuous change which is inherited. Geneticists, for the most part, subsequently have tended to limit the use of the term to point-mutations, that is, to changes at single gene loci. Chromosome breakages, deletions and translocations are classed as mutations in a more general sense. Changes in chromosome number, polyploidy and aneuploidy, however, although they arise just as suddenly as other anomalies in a lineage, are usually considered as a separate class of phenomena. The distinction is to some extent arbitrary and terminology should not be allowed to cramp investigations into all types of spontaneous hereditary changes. Thus we can conveniently classify together all mutations and allied phenomena in man under the three broad headings of point-mutations, structural alterations and numerical changes in the chromosomes. The first task is to establish the frequencies of these occurrences in known instances. The second task is to study the circumstances in which these events are most liable to occur with a view to establishing their causation.

Measurement of Spontaneous Point-mutation Rate at Specific Loci

Estimation of mutation rate in man, in relation to any given hereditary trait, depends upon ascertaining three things: the incidence of the trait in the general population, the manner of its inheritance and the fitness of the genotypes concerned. These phenomena are not necessarily constant over the long series of generations during which natural selection has been acting. As seen at the present day, they only give us the first clue to conditions which govern genetical equilibrium in human populations.

A point-mutation can be defined as a change confined to a chromosomal region small enough to be considered the locus of a single gene. Two standard methods of approach are in use for ascertaining point-mutation rates, the direct and the indirect.

Direct Observation

The most favourable circumstance for estimating mutation rate occurs when a gene is detectable with certainty or regularity in heterozygotes. Instances of fresh mutation can then be observed in families where a gene shows in an offspring although it was not present in either parent. The ideal kind of regular dominance required for this is rarely (perhaps never) found in human genetics. Man is a wild species under natural selection unlike laboratory stocks, and consequently most single gene effects, especially those shown in heterozygotes, are subject to modification. Even with the most reliable characters, such as blood group antigens and serum proteins, suppression is possible by gene interaction (Levine, Robinson, Celano, Briggs and Falkinburg, 1955; Harris, Robson and Siniscalco, 1959); such events could easily be misinterpreted by the unwary as evidence of mutation.

The situation for sex-linked genes is quite favourable, theoretically, for direct observation of fresh mutation because modification of a character shown in hemizygous males is slight. Families will be observed in which there are no affected male relatives and consequently in which the probability is high that the disease in the propositus is due to fresh mutation.

For recessive diseases the problem of estimating mutation rates is much more difficult because heterozygous carriers are detectable only in special circumstances. Where special techniques have been developed for identification of carriers the problem can be theoretically resolved into one of detection of mutation for a dominant condition, as demonstrated by Vanderpitte, Zuelzer, Neel and Colaert (1955) for sickle cell trait. Direct observation of cases of recessive diseases due to fresh mutation is very unlikely to be possible because only a very small proportion of cases of a recessive trait in a given generation can be attributed to fresh mutation in a parent. For diseases in which a single gene is only a part cause and in which

environment has a great effect upon manifestation, the contribution of spontaneous mutation is likely to be even less significant. The same applies to conditions due to the interaction of many genes and to graded characters in general. For none of them can mutation rates be directly determined.

The Indirect Argument

When the total effects of a gene are very disadvantageous an indirect line of argument can be used for estimating mutation rate, even though the gene may not be manifest in the heterozygous state. Principles on which the indirect estimation of mutation rates can be based were enunciated by Haldane (1932a). The assumption can be made that the human population is in a state which is very near to genetical equilibrium under natural selection. It is supposed that disadvantageous genes could not persist in the population unless their extinction by selective mortality were completely balanced by the persistent recurrence of fresh mutation (see Appendix).

In the case of dominant or sex-linked characters associated with very high mortality, the direct measurement of mutation rate can be supplemented, and its plausibility greatly strengthened, by the indirect argument. The best situation for this combination occurs in the case of a very deleterious dominant trait. This is a rare circumstance. If the disease is not very lethal, there will be difficulty in measuring the unfitness conferred by the gene; if it is very lethal, there is difficulty in proving the dominant mode of inheritance, as it will seldom last even for two generations. Sometimes the problem might be solved for a locus, which had several different known alleles, some producing milder and others severer types of disease. Then, every severe case observed will have been an example of mutation to a lethal allele. This clearly occurs in epiloia, in neurofibromatosis and in chondrodystrophy. For mild alleles, which last for several generations, the proportion of cases due to fresh mutation is correspondingly smaller.

Estimates which are entirely indirect are untrustworthy, but they have actually been made for a variety of genes recognised only by their homozygous recessive effects. One cause of uncertainty with recessive traits is that allowance has to be made for the results of

inbreeding. Another, more serious, source of error is that genetical equilibrium can be maintained not only by mutation but also by slightly advantageous effects in heterozygotes. That is to say, on the balance, the total effect of a gene may be much less unfavourable than appears from studying abnormal homozygotes. In such circumstances the indirect estimate of mutation rate will give much too high a value.

Some Standard Estimates of Point-mutation Rates

Point-mutation rates have been calculated for quite a large number of loci in man. It is preferable to express them in terms of loci per generation, if we wish to avoid controversy, because slightly different forms of the diseases concerned can be accounted for by the same allele or by different alleles. When several very closely linked genes give rise to a pseudoallelic system, the real mutation rate for each separate element is lowered by a factor depending upon the number of elements in the complex.

Dominants

The most exact estimates for supposedly single loci are probably those for very deleterious dominant traits (see Table 1). Allowing for the probability that more than one disease entity may be classified under each heading, they must be thought of as maximal values.

Owing to the classification of more than one type of chondrodystrophy under the same heading the rate given is likely to be considerably too high. According to Grebe (1955) there are several clinical types; and some cases may be due to recessive genes. Furthermore, these types may have different mutation rates. The same lack of uniformity is present in neurofibromatosis where estimates may represent the sum over several distinct loci.

Another dominant condition which apparently has a relatively high mutation rate, namely, retinoblastoma, occurs perhaps not infrequently as a phenocopy (Vogel, 1954) or as a somatic mutation not transmissible to the next generation. The same idea could be applied also to other conditions listed in Table 1, such as microphthalmos.

TABLE 1

Estimates of Spontaneous Mutation Rates at some Human Autosomal Loci: Dominant Diseases

Trait	*Mutation Rate per million loci per generation*	*Region*	*Source*	*Date*
Epiloia	8	England	Gunther and Penrose	1935
Chondrodystrophy	45	Denmark	Mørch	1941
Chondrodystrophy	70	Sweden	Böök	1952
Aniridia	5†	Denmark	Møllenbach	1947
Microphthalmos without mental defect	5	Sweden	Sjögren and Larsson	1949
Retinoblastoma	15	England	Philip and Sorsby*	1947
Retinoblastoma	23	U.S.A.	Neel and Falls	1951
Retinoblastoma	4	Germany	Vogel	1954
Partial albinism and deafness	4	Holland	Waardenburg	1951
Multiple polyposis of the colon	13	U.S.A.	Reed and Neel	1955
Neurofibromatosis	100	U.S.A.	Crowe, Schull and Neel	1956
Arachnodactyly	6	N. Ireland	Lynas	1958
Huntington's chorea	5	U.S.A.	Reed and Neel	1959
Acrocephalosyndactyly	3	England	Blank	1960

* Unpublished.

† This estimate differs by a factor of 2 from that given by the author but it is based on his material.

The indirect argument, which supports all these estimations, can only be used when there is strong selection against the gene studied. Theoretically, it should be possible to obtain mutation figures for several blood antigens, e.g. *ABO* or *MNS*, but selection against any of these genes is too slight and indefinite to be used as direct support for the mutation hypothesis. On the other hand, the indirect argument can be extended to cover certain cases in which the combination of several genes at different loci is lethal or very deleterious. Thus a lethal condition, caused by the simultaneous presence of two heterozygous genes, will imply that each of the genes concerned mutates frequently enough to make good the loss occasioned when it occurs in conjunction with the other.

Taking all these considerations together we can reasonably assume that the mutation rates for loci giving rise to dominant genes, though somewhat too high, are of the right order of magnitude. It seems that, for most of these dominant diseases, the rate should be considered to be not far from 5×10^{-6}.

One further reservation has to be made because there is evidence that mutations can occasionally occur in a whole section of the gonad (MacKenzie and Penrose, 1951). In such circumstances the parent would be a mosaic for the mutant gene and several offspring could be affected. If this happened often, the true mutation rate would be less than that inferred from enumeration of all cases. An even more serious problem is posed when the possibility of delayed mutation is entertained. The spontaneous appearance in collateral relatives of a rare dominant trait, such as ectrodactyly or retinoblastoma is, however, probably best explained by assuming variable manifestation (Vogel, 1958; Macklin, 1959).

Sex-linked Loci

The prevalence in man of sex-linked diseases which are very lethal is difficult to explain except on a hypothesis of recurrent mutation. Direct evidence based upon observed low incidence of hæmophilia in sibships and in maternal collateral relatives also supports this explanation. The matter has been repeatedly investigated by Haldane (1946). Sex-linked diseases are identified by pedigree studies and by their occurrence in males only but, by this process, some autosomal cases may occasionally be incorrectly included. A characteristic difficulty is the exclusion of autosomal sex-limited conditions. Haldane (1955) considered that mutation of sex-linked genes was of more frequent occurrence in males than in females, but this conclusion has not been substantiated (Smith and Kilpatrick, 1958).

In the standard examples of hæmophilia and sex-linked muscular dystrophy, mutation rates have been estimated several times but always on the assumption that, in each disease, there is only one locus involved. These rates, as shown in Table 2, are considerably higher than the direct estimates for autosomal dominants. Perhaps the X-chromosome is peculiar in that it has many complex loci or distinct loci with similar effects.

TABLE 2

Estimates of Spontaneous Mutation Rates at some Human Sex-linked Loci

Trait	*Mutation Rate per million loci per generation*	*Region*	*Source*	*Date*
Hæmophilia . .	20	England	Haldane	1935
Hæmophilia . .	32	Denmark	Andreassen	1943
Hæmophilia . .	27	Switzerland and Denmark	Vogel	1955a
Pseudohypertrophic muscular dystrophy	95	U.S.A.	Stephens and Tyler	1951
Pseudohypertrophic muscular dystrophy	60	N. Ireland	Stevenson	1958
Pseudohypertrophic muscular dystrophy	43	England	Walton	1955
Pseudohypertrophic muscular dystrophy	47	England	Blyth and Pugh	1959

Recessive Traits

A recessive trait in man can be defined as one which depends upon a gene in homozygous form. There may be mild manifestations detectable in heterozygotes (as, for example, in thalassæmia, galactosæmia and cystinuria), but the disease in the homozygote is the effect with which we are concerned. The indirect estimates of mutation rates for recessive diseases shown in Table 3, assume that

TABLE 3

Indirect Estimates of Spontaneous Mutation Rates on the Assumption of Recessive Inheritance

Trait	*Mutation Rate per million loci per generation*	*Region*	*Source*	*Date*
Juvenile amaurotic idiocy	38	Sweden	Haldane	1939
Albinism . . .	28	Japan	Neel *et al.*	1949
Ichthyosis congenita .	11	Japan	Neel *et al.*	1949
Total colour blindness .	28	Japan	Neel *et al.*	1949
Infantile amaurotic idiocy	11	Japan	Neel *et al.*	1949
Amyotonia congenita .	20	Sweden	Böök	1952
Epidermolysis bullosa .	50	Sweden	Böök	1952
Microcephaly . .	49	Japan	Komai *et al.*	1955
Phenylketonuria . .	25	England	Penrose	1956a

the heterozygote is neutral in its effect upon fitness. If the heterozygous states corresponding to these recessive diseases were deleterious, the mutation rate values would have to be increased. Conversely, if heterozygotes were slightly favourable, the values would have to be reduced. A very slight amount of heterozygous advantage is sufficient to keep a rare recessive lethal in stable genic equilibrium in the absence of mutation so that these indirect calculations of mutation rate very easily lead to exaggerated values. This is an important principle worthy of careful consideration.

Most well-known recessive traits cannot easily be supposed to have arrived at their existing levels of gene frequency (e.g. 1/100 for phenylketonuria) by chance or by "drift". The situation for commoner genes is even more striking. For thalassæmia and sickle cell trait (Neel, 1951b), cystic fibrosis (Goodman and Reed, 1952), spastic diplegia (Böök, 1953) and schizophrenia (Penrose, 1956a) improbably high mutation rates of the order of 1 per 1000 have been postulated. These common recessive traits could not easily have established themselves unless the heterozygotes had some advantage. The advantages may have been local ones in the distant past, for example, ability to withstand infections, plagues, famines, extreme climates, and so on. It is not necessary to postulate any virtue in the heterozygote as such. It could be sufficient if the mutant allele had, by chance, been favourable at one epoch and unfavourable at another epoch, in different circumstances or at different stages of the same life cycle.

It has been suggested by Haldane (1939) that indirect mutation rate estimates for recessive traits are sometimes too low. The argument used is that the true incidence, which recurrent mutation would theoretically balance, has in the past been much greater than it is at the present time. This is held to be likely because inbreeding, which facilitates the appearance of recessive diseases, has been gradually diminishing for many decades in all civilised communities. It is doubtful if Haldane's view represents the true state of affairs. The incidence of rare recessive traits in man is extremely irregularly distributed. In Europe, infantile amaurotic idiocy is almost confined to Jewish communities, as also is pentosuria. Thalassæmia has a concentration in the Po delta in Italy. Phenylketonuria, on

the other hand, does not occur among Jews. Sickle cell anæmia is common in Africans. Juvenile amaurotic idiocy is commonest in Sweden and acatalazæmia has been found only in Japan. These facts suggest that recessive characters are probably connected with heterozygous advantage at one epoch or another. If mutations were not extremely rare, the same set of recessive diseases would appear in all communities, or at least in all inbred communities, throughout the world.

To sum up the discussion on spontaneous mutation rate, my view is that, for a variety of reasons, most of the estimated rates already calculated are too high.

Incidence of Spontaneous Chromosomal Aberrations

The effects of chromosomal anomalies such as small deletions are not likely to be distinguishable, at the present time, from gene mutations. Thus conditions like achondroplasia and acrocephalosyndactyly may be assumed to be gene mutations unless and until a chromosomal change responsible for them is discovered. The effect of an inversion might be extremely difficult to identify. On the other hand, a translocation, by giving rise to a proportion of unbalanced gametes, might show in the offspring of balanced translocated parents. This mode of transmission of abnormalities was demonstrated by Snell and Picken (1935) in mice. Some pedigrees of human malformations are strongly suggestive of the occurrence of similar phenomena in man. That is to say the transmission, through normal members of a family, of the same defect through several generations. This was known to happen in several conditions, among them anencephaly, spina bifida and mongolism, as noted by Haldane (1939) and by Penrose (1939). The first cytological indication of such a process came from the observations of Polani, Briggs, Ford, Clarke and Berg (1960) on a case of mongolism. The frequency of spontaneous occurrence of translocations in man cannot yet be guessed but they may be more prevalent than formerly supposed. The same applies to somatic chromosome fragmentation, which has now been proved to occur in the X-chromosome, as described in Chapter 2.

The frequencies of examples of aneuploidy, that is alterations in

chromosome number, are more easily obtained because they give rise to recognisable abnormalities, many of which are not inconsistent with a moderate degree of health. Even so, to obtain accurate estimates, the incidence at birth must be ascertained. Much information is available about the frequency of mongolism at birth. The incidence in England is perhaps as high as one in 660 births, though in Japan it may be considerably lower than this.

Though the estimates given in Table 4 are probably fairly reliable, they are subject to errors in diagnosis; variations in different populations and areas cannot yet be accepted as real. As diagnostic techniques improve, estimates should become available from all over the world and they will be of great interest. In the example of female sex chromatin in the male we can assume that the majority of instances are cases of Klinefelter's syndrome and, similarly, in mongolism we can assume that most cases are instances of simple trisomy. Since these conditions are associated with a very low fertility indeed it may be assumed that a change producing aneuploidy in the parental germ cells has occurred in the great majority of the cases observed. That is to say, they are mostly instances of primary non-disjunction, not secondary non-disjunction or translocation. It is noteworthy that the frequencies of these changes are much higher than point-mutation rates given in Tables 1, 2 and 3; indeed they are roughly 100 times as frequent. Other types of aneuploidy may also be common but some of them, like the monosomy in Turner's syndrome and trisomy of large chromosomes, may be prone to miscarry at early stages of development.

Induced Mutation

Although mutations are referred to as spontaneous changes they must have causes and certain environmental conditions are known to facilitate them, such as exposure to heat, ionizing radiations and any of a large variety of chemical substances. Many attempts have been made to investigate in man the mutagenic effects of exposure to radiation. The task of demonstrating any unequivocal increase in an exposed population is, however, extremely difficult. The initial problem of ascertaining the basic spontaneous rates is far

TABLE 4

Incidence at Birth of Conditions Associated with Aneuploidy

Condition	*No. Observed*	*Population of Births*	*Frequency*	*Incidence per Thousand Births*	*Population*	*Source*	*Date*
Mongolism . .	6	3,818	1/636	1·57	U.S.A.	Jenkins	1933
	18	13,964	1/776	1·29	England	Malpas	1937
	32	27,931	1/873	1·15	U.S.A.	Parker	1950
	130	67,645	1/520	1·92	Switzerland	Hug	1951
	107	71,521	1/666	1·50	England	Carter and MacCarthy	1951
	52	39,788	1/765	1·31	Denmark	Øster	1953
Female sex chromatin in a male . .	5	3,715	1/743	1·35	Canada	Moore	1959