ON THE INTERACTION OF HEREDITY AND ENVIRONMENT IN THE STUDY OF HUMAN GENETICS (WITH SPECIAL REFERENCE TO MONGOLIAN IMBECILITY).

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CONTENTS.

1. Introduction.

Most studies of human genetics which have hitherto been made have not taken into consideration the full significance of the environmental influences which may modify the data from which numerical conclusions have been drawn. Some early geneticists, like Bateson (1), confined their attention to what appeared to be simple physical characters, like brachydactyly and eye colour. In later studies, however, now that the field of such simple phenomena is becoming exhausted, attacks have been made by the same methods on problems of an entirely different nature. Studies in the inheritance of acquired diseases, like tuberculosis, would be cases in point. And, while few people would be foolish enough to suppose, for example, that a study of affected and normal members of tuberculous families would give numerical results which could be utilised as those of brachydactyly, it is surprising how many observers have treated the more subtle phenomena of mental disease in ways which are open to severest criticism (2). It is, moreover, probable that a very large class of human characteristics of a directly physical nature are determined to a considerable extent by environmental influences, although they may also give evidence of being phenomena

suitable for genetic investigation. Jennings[1] has clearly summed up the position in his recent book on the Biological Basis of Human Nature (3). But, although such problems are well understood in experimental genetics, little serious attempt has so far been made to tackle them as far as human beings are concerned.

The present paper sets out to describe some methods which may be of use in making such an attempt, and the example of "mongolian" imbecility is taken to show how the methods can be applied in practice.

2. Methods of dealing with a varying environment.

Supposing that we required to know the manner of inheritance of susceptibility to such a disease as cholera, the simplest method would be to observe families living in one place who drank, unboiled, the water which became polluted, and to note which individuals escaped infection and which did not.

In this case the environment could be regarded as constant, assuming that allowance did not have to be made for age and sex of the individuals concerned. But any members of the family living in *another place*, where the water was not polluted, would have to be excluded from the survey. It would be easy enough then to take those parts of the families which lived in the polluted district and drank the water, to obtain from them the numerical ratios of susceptible children born to non-susceptible or susceptible parents, and so to determine the type of inheritance involved. The usual allowance for the exclusion of fraternities in which no affected member occurred would of course have to be made where necessary.[2]

[1] *The Biological Basis of Human Nature*, by H. S. Jennings (1930). Cf. Chap. v, p. 130. "Certain characteristics in the fruit-fly illustrate similar relations between the effects of genes and the effects of environment. *Drosophila* is commonly grown for experimental purposes in bottles containing decaying banana, the atmosphere within the bottles being moist. When so grown, certain individuals are defective in that the abdomen is ill-formed. This abnormality is found to be due to a defect in a gene of the *X*-chromosome, so that it shows a sex-linked inheritance, the abnormality being dominant.

"But the abnormality also depends on the environment. It appears, in the individuals having the defective gene, only if they are grown in a moist atmosphere. If grown in a dry atmosphere, the individuals are normal, even though they contain the defective gene. The production of the abnormal abdomen thus requires both a certain type of gene and a certain type of environment."

[2] The formula for calculating the expected number e of affected offspring when the size of the fraternity is s, but where these fraternities are selected by the presence of at least one affected member is

$$e = \frac{sn_s p}{1-(1-p)^s},$$

Evidently conditions will not often be as favourable as this for investigating the behaviour of human beings under a constant environment. In studying the inheritance of susceptibility to tuberculosis, for example, it may not be easy to ascertain how far environment has encouraged the manifestation of the disease in any given person. But the problem, though difficult, is not insoluble, since it may be possible to arrange different families, or parts of families, in an order of increasing intensity of their environments. The true proportion of susceptible individuals in these groups of families, or parts of families, will then be approached asymptotically as the environmental agency affecting successive groups of individuals becomes more and more universal. An objection to this method of procedure is that the cases suitable for inclusion in any group become fewer as the criteria of effective environment become more stringent. Thus the most important conclusions are only drawn from a small part of the whole data studied. But this only means that a much greater amount of material has to be collected for this type of study than was considered necessary for examining traits where environment is thought to play no part.

Difficulty may also be experienced in deciding under what circumstances the environmental effects are considered to be greater in one group than in another. It would clearly be wrong to assume that increased familial incidence was in itself a criterion of increased environmental influence. This assumption would simply beg the question. But a measure of the strength of the environment necessary to produce the disease, which would be free from this objection, could be obtained by incidence in the community of those persons who were the only ones known to be affected in their families.

One of the most important kinds of environment to which human beings are subject affects them during their pre-natal existence. Evidence of its significance can be obtained by observing the way in which certain diseases have a preference for first-born children. Still(4) reported that just under 50 per cent. of patients suffering from congenital pyloric stenosis were first-born, and the same is probably true for some other congenital defects. More striking perhaps are those features which tend to affect late-born children. Certain forms of mental deficiency seem to come into this category, and, most notably, mongolian imbecility.

where p is the true ratio of affected to total offspring and n_s is the number of fraternities of size s.

The expected total number of affected persons is the sum of the expected numbers of persons in each set of fraternities containing the same number of members.

This disease has recently occupied a great deal of attention, and much evidence has been adduced showing that the age of the mother at the birth of the child is an important factor in its causation, the age of the father being of less moment. This fact gives us an exceedingly useful criterion for judging the relative strength of an environmental agency for different groups of persons. Table I shows the incidence of the condition at different maternal ages.

The material which forms the subject of Tables I–V, IX and X consists of 82 families studied in the course of research work at the Royal Eastern Counties Institution. The cases of familial incidence were discovered quite accidentally in the course of intensive family investigation. They are excluded from Table I for reasons stated above.

The table shows clearly that the incidence of mongolism increases with the maternal age, the only exception being that there is a greater

TABLE I.

Distribution of children at different maternal ages in 78 *fraternities containing* one mongolian imbecile only.

	Maternal age (years)							
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	Total
Total No. of children (including miscarriages)	7	61	103	98	84	77	12	442
No. of mongolian imbeciles	1	6	5	8	19	34	5	78
Percentage incidence of mongolism	14·3	9·8	4·9	8·2	22·6	44·2	41·7	17·7

The incidence shown in the last column is, of course, determined here by the reciprocal of the average size of the fraternity, which is 5·66 individuals.

incidence among pregnancies before the age of 25 than between the ages of 25 and 34. There seems in fact to be a definite inverse relation between the frequency of the condition and the child-bearing activity of the mother, and this effect is even better shown if the incidence of affected children is judged by reference to the number of unaffected children born at different maternal ages, as will be seen later (Table IX).

The evidence of some pre-natal environment being a cause of mongolism is so strong that it has led some authors, notably Goddard (2), Clark (5) and Van der Scheer (6), to the belief that it is the only cause. There is, however, strong evidence on the side of those persons who hold that the condition is due to heredity. Apart from the rather infrequent occurrence of more than one affected child in the same fraternity, or in more distantly related members of the same family, twins have many times been observed where one was normal and the other affected. There

was one example of this in the present series. Thus there seems to be a good *prima facie* case for regarding susceptibility to the condition as hereditarily determined.

TABLE II.

Familial incidence of mongolism (1). (82 *families.*)

Size of fraternity (s)	No. of fraternities (n_s)	No. of persons affected	Expected No. affected (e) $e = \frac{sn_sp}{1-(1-p)^s}$, $p=1/50$
1	6	6	6·00
2	9	9	9·12
3	17	17	17·35
4	6	6	6·19
5	4	4	4·16
6	8	8	8·40
7	5	6	5·31
8	6	7	6·43
9	7	7	7·57
10	6	7	6·56
11	1	2	1·10
12	1	1	1·11
13	3	3	3·37
14	2	2	2·27
15	1	1	1·15
	82	86	86·09

The required value of p is nearly 1/50, or about 1·9 per cent.

The number of individuals in these fraternities who are not known to be affected is 392, and is made up as follows:

Considered to be unaffected as regards mongolism ...	318
Miscarriages, stillbirths and deaths in infancy under 1 year	74

TABLE III.

Familial incidence of mongolism (2). (69 *partial fraternities.*)

Complete or partial fraternities *occurring after the maternal age of* 30 *years.*—They are selected by the presence of at least one mongolian imbecile born during this period.

Size of partial fraternity	No. of partial fraternities	No. of persons affected	Expectation of No. affected (1) $p=1/32$	(2) $p=1/25$
1	10	10	10·00	10·00
2	9	9	9·14	9·18
3	13	13	13·42	13·54
4	9	10	9·43	9·56
5	9	10	9·58	9·75
6	10	10	10·81	11·05
7	4	6	4·39	4·51
8	1	1	1·11	1·15
9	4	4	4·53	4·68
	69	73	72·41	73·42

The required value of p lies between 1/32 and 1/25. It is approximately 3·7 per cent.

Number of individuals in these fraternities considered to be unaffected	163
Number of miscarriages, stillbirths and deaths under the age of 1 year	44

Owing to the convenient fact that the environmental influence increases in an orderly way, it is possible to divide up families containing

mongolian imbeciles into groups of partial fraternities, and to arrange them in a series in order of increasing strength of environment. This has been done in the Tables II, III, IV and V. It will be seen that there is an increasing familial incidence which may be tending to an upper limit of magnitude, though with so few cases we have little exact information where this limit lies. It is obviously useless to try and make inferences

TABLE IV.

Familial incidence of mongolism (3). (62 *partial fraternities.*)

Fraternities or partial fraternities *occurring after the maternal age of* 35 *years,* and selected by the presence of at least one mongolian imbecile occurring during this maternal age period.

Size of partial fraternity	No. of partial fraternities	No. of persons affected	Expected No. affected $p=1/20$
1	15	15	15·00
2	9	9	9·23
3	19	20	19·99
4	11	12	11·86
5	4	5	4·43
6	2	2	2·27
7	2	2	2·32
	62	65	65·10

The required value of r is a little less than 1/20, and is about 4·9 per cent.

Number of individuals considered to be unaffected 85
Number of miscarriages, stillbirths and deaths under the age of 1 year 30

TABLE V.

Familial incidence of mongolism (4). (41 *partial fraternities.*)

Partial fraternities *occurring after the maternal age of* 40 *years,* and selected by the presence of at least one mongolian imbecile.

Size of partial fraternity	No. of partial fraternities	No. of persons affected	Expected number affected	
			(1) $p=1/15$	(2) $p=1/16$
1	20	20	20·00	20·00
2	11	11	11·46	11·35
3	9	10	9·67	9·13
4	1	1	1·11	1·03
	41	42	42·24	41·51

The required value of p lies between 1/16 and 1/15; it is about 6·4 per cent.

Number considered to be unaffected 23
Number of miscarriages, stillbirths and deaths under 1 year 8

about the manner of inheritance of the disease without taking the environmental effect into account, as has been done by Macklin (8). The figures also show how important it is to make tests of this kind before giving a verdict on numerical ratios obtained from the study of affected siblings in any condition where environmental influence may be suspected.

3. METHODS OF ALLOWING FOR MORTALITY OF AFFECTED INDIVIDUALS.

A very important way in which environment may alter numerical genetical data is by the exclusion of affected cases from observation by selective mortality; that is to say, the affected individuals may die before they are diagnosed.

The figures obtained by the observation of cases affected by a sub-lethal condition may be seriously falsified by deaths of infants before diagnosis is made, or even before it is possible. Several methods, however, can be devised for estimating, at any rate roughly, how much a given ratio of affected individuals to normal may be altered by a "pre-diagnosis" mortality.

If we have direct means at our disposal for finding the mortality rate of the class of affected individuals the matter is comparatively easy, but this is not usually the case, and the best that can be discovered is the relative mortality of the members of the affected class who are recognised and members of the general population. And it is required to discover how far the number of affected persons in a family has been depleted by their selective mortality.

A problem in inverse probability is thus set which can be solved as follows.

Let A be the true number of affected individuals in a group of fraternities who are subject, during a given unit of time, to a mortality ϕA.

Let U be the true number of unaffected individuals subject, in a given unit of time, to a mortality ψU.

Then the relative mortality A to U is $\frac{\phi}{\psi}$; call this R.

Now call the observed numbers of affected individuals a, and the observed number of individuals who die before diagnosis is made one way or the other, x. If u represents the number of individuals who are observed to be unaffected, the following relations hold good:

(i) $A + U = a + u + x =$ the total number of individuals.

(ii) $A - \phi A = a$.

(iii) $U - \psi U = u$.

From these equations A can be expressed in terms of the observed quantities, R, a, u and x, thus:

(iv) $A^2(R-1) + A[Ru + a - (R-1)(a+u+x)] - a(a+u+x) = 0$,

and when A has been evaluated U can be found from (i).

Uusually it is simplest to regard all these numbers as percentages, thus $(a + u + x) = 100$. Sometimes a is only known as a fraction or percentage, as when correction has been made for selection of fraternities by their having at least one affected member. Under such conditions all the numbers must be expressed as fractions or percentages. (In Tables II–IV above, $\frac{a}{a+u+x} = p$[1].)

Any conclusion drawn concerning the probable nature of unknown individuals from such an argument as this will have to be consistent with what is likely from other sources of information. For example, if we assume that a certain number of infantile deaths in any group is due to a sub-lethal trait, the incidence of such deaths must be in excess of that where, under the same conditions otherwise, the specific trait is absent. For example, it is well known that, in families where the children have congenital syphilis, infantile deaths and miscarriages are much more frequent than among non-syphilitic families: and, if we know how much more frequent such events are, we have a method of checking the result which would be obtained by applying the above formula. Generally speaking, all possible arguments in favour of regarding unknown individuals as affected must be applied before such a risky inference can be made.

To exemplify the use of the methods under discussion, we will again take the data supplied by the study of mongolian imbecility.

In the first place the condition may be regarded as sub-lethal since the death-rate among affected individuals is very high. They are susceptible to all kinds of infectious diseases besides frequently having congenital physiological defects which render them unlikely to survive, *e.g.* patent inter-ventricular septum. Furthermore, it is usually not before the child is a year old that the condition is recognised, and even if it is the parents are rarely informed.[2] Cretinism is a frequent early diagnosis.

Various possibilities are open for the evaluation of the ratio R, according to the type of data available. Where the ages at death of a group of cases are known, provided that such a group is sufficiently representative, this group of cases can be regarded as a complete popu-

[1] It is commonly assumed, in genetical studies, that $\frac{A}{U} = \frac{a}{u}$. This is only true if $R = 1$ or $x = 0$.

[2] The condition *can* be diagnosed much earlier, but, especially in country districts and among the poorer classes, this is unusual. In the present series of 86 cases, the mother was only definitely aware of the diagnosis in 4 cases before the child was 1 year old.

lation, and its death-rate at different ages compared with that in the general population. The figures given by Brousseau (7) of American mongols can be treated in this way, and while they are not strictly comparable with the general English population, a rough idea can be obtained from them of the value of R, which averages out at about 10, *i.e.* the mortality of mongolian imbeciles is, at all ages above 12 months, about ten times the normal (cf. Table VI).

TABLE VI.

Comparative mortalities of mongols and normals at different ages.

(For purposes of this assessment those persons whose ages at death are recorded are regarded as constituting a complete community—representative of the whole community of similar individuals.)

	(1) Mongols (Brousseau)		(2) General Population (Registrar-General's Report 1930, England and Wales)		
Age	No. living	No. of deaths at this age period	No. living	No. of deaths at this age period	Ratio, Mortality (1) / Mortality (2)
1–4	*134**	35	*4165**	168	6·47
5–9	99	24	3997	79	12·27
10–14	75	24	3918	48	26·12
15–19	51	14	3870	85	12·50
20–24	37	16	3785	105	15·59
25–29	21	9	3680	106	14·88
30–34	12	6	3504	106	16·53
35–39	6	2	3398	120	9·44
40–44	4	4	3278	149	22·00
Total	439	134	33595	966	10·62

From this table it is inferred that the relative mortality of mongols, as compared with the general population (who are for the most part unaffected), is about 10 : 1.

* These figures at the top of the columns represent the total number of deaths, *i.e.* the total community under consideration.

A somewhat better method can be applied to the data, recorded by Dr Brushfield[1], of mongols admitted to the Fountain Mental Hospital in London, and it gives a similar result (Table VII).

Comparison of the figures in the two columns on the right shows that the mortality rate of mongols is about ten times as great as that of the general population.

The most accurate comparison which I have been able to make to determine this ratio was afforded by a detailed survey of the records of patients in the R.E.C.I. during the last 10 years. The average yearly populations of mongols and non-mongols were compared as regards their average yearly death-rates, for males and females of all ages above 4 years (Table VIII).

[1] These records are in the library of the Royal College of Surgeons, London.

The conclusion is much the same as previously ascertained, namely that the relative mortality of mongols to the general population is nearly 10 to 1. The death-rate among mongols is, moreover, about six times as great as that among other types of mental defectives living under the same conditions.

A curious feature of the figures in Tables VII and VIII is the greater mortality of mongol females than males. My data are not extensive enough

TABLE VII.

Mortality of mongols from Dr Brushfield's data.

	Ages at time of examination	No. of cases	No. which died within 4 years of examination: Observed	Expected
Males:	below 5 years	36	21	3·9
	5 to 9 years	59	20	0·7
	10 to 14 years	25	2	0·2
	Total	120	43	4·8
Females:	below 5 years	25	17	2·2
	5 to 9 years	47	13	0·4
	10 to 14 years	18	1	0·1
	Total	90	31	2·7

The expected number of deaths is obtained by multiplying the yearly mortality rate in the general population (1921–25) for each age group by 4 times the number of cases.

TABLE VIII.

Average yearly mortality, R.E.C.I., 1921–31.

	Males	Females	Total
Mongols, R.E.C.I., per 1000	95·6	114·5	101·2
Non-mongols, R.E.C.I., per 1000	16·4	18·6	17·3
Relative mortality (mongols/non-mongols)	*5·83/1*	*6·15/1*	*5·85/1*

Average yearly mortality (Registrar-General's Report, England and Wales), 1921–31

	Males	Females	Total
(Standardised) per 1000 living ...	11·8	9·6	10·6
Relative mortality (mongols/general population)	*8·0/1*	*11·9/1*	*9·5/1*

to decide whether or not this is generally true. But it raises the issue that a preponderance of one or other sex in affected persons may be due to environmental differences between the sexes which cause differential mortality, and not to any question of sex-linkage in inheritance.

Actually it is often stated that male mongols are much more frequent than females(9). This does appear to be true when those cases under institutional care are studied, but these are only a small proportion of all the cases living. Females are less trouble to manage than males and

can be useful in the home, so they do not drift so much into institutions and are altogether less likely to be noticed. They may also be less viable than the males. In the present series, out of 86 cases, the institutional ones numbered 30 males and 11 females, and those not under institutional care numbered 28 males and 17 females. Among the 392 brothers and sisters of these 86 cases there were 187 males, 155 females and 50 of unknown sex. It does not appear, from these figures, that the excess of male cases over females is of genetic significance[1].

Although it may perhaps be legitimately inferred that the relative mortality rate among mongols as compared with normals is the same below the age of 1 year as it is above it, it does not necessarily follow that, since there is a high infantile mortality, the pre-natal mortality, as expressed by miscarriages and stillbirths, is also high. In congenital syphilis both propositions are true, and it is quite possible that they are both true for mongolism.[2] Van der Scheer (6) reported that, in his experience, miscarriages frequently occurred to mothers of mongolian imbeciles, but not more frequently than to mothers of other idiots. He did not, however, consider the difference in the proportion of miscarriages occurring at different maternal ages. He mentioned that abnormal bleeding in pregnancy and premature labour were not uncommon. As far as my own observations go, I can substantiate the latter findings. In over 10 per cent. of the cases in my series, threatened abortion occurred, and about 5 per cent. of the affected children were premature.

As regards miscarriages the position is always a little uncertain, since, however careful the investigation may be, these occurrences are very

[1] Taking together all the cases of mongolism which have been ascertained at the present moment in two of the Eastern counties, the numbers are as follows:

	Males	Females
Living in the R.E.C.I.	24	7
On R.E.C.I. register but living at home	2	4
Living at home not under institutional care	77	73

[2] This assumption is backed up by the curious fact that, although cases of like-sexed twins, both affected, have been observed, there is no instance on record of twins both affected and of different sexes. The explanation seems to be that, while in the case of "identical" twins neither is more likely to miscarry than the other, in the case of twins which are both affected but binovular, one twin nearly always miscarries. I have, in the present series of histories, two possible examples. In one of these a miscarriage occurred in the fourth month without terminating pregnancy, and, later, a mongol child was born; in the other instance, a stillbirth occurred and, next day, a mongol twin was born. It seems unlikely that a normal child would miscarry and leave a defective one alive *in utero*. It is also unlikely that one monozygotic twin could miscarry without the other's doing so. The suggested explanation is that the miscarriage or stillbirth represented a binovular mongol twin.

liable to be overlooked, and no normal families are available for comparison. What may be a significant fact, however, is shown in Table IX.

The ratios showing the incidence of affected cases and unknowns are calculated on the basis of the distribution of unaffected children

TABLE IX.

Analysis of 82 *fraternities.*

	Maternal age (years)					
	Below 25	25–29	30–34	35–39	40 and above	Total
Unaffected (non-mongols)	51 *1·00*	92 *1·00*	84 *1·00*	54 *1·00*	37 *1·00*	318 *1·00*
Undiagnosed:						
(1) Miscarriages	4	10	9	11	12	46
(2) Stillbirths and deaths under 1 year	10	5	4	5	4	28
	14 *0·27*	15 *0·18*	13 *0·15*	16 *0·33*	16 *0·43*	74 *0·23*
Affected (mongols)	7 *0·14*	5 *0·05*	9 *0·11*	22 *0·41*	43 *1·16*	86 *0·27*

The figures italicised give the ratios of *undiagnosed* and *affected* individuals to *unaffected* persons in each age group—the number of *unaffected* persons being regarded as unity.

Of the 74 undiagnosed individuals, 46 were miscarriages, 16 were stillborn or died under a week. The remaining 12 lived more than 1 week, but less than 1 year.

TABLE X.

Estimation of the proportions of affected persons in complete and partial families, on the assumption that the relative pre-natal and infantile mortality of mongols to non-mongols is as 9 to 1.

	u	x	a ($a = p \times 100$)	Estimated values of U and A calculated for $R = 9$: U	A
82 complete fraternities (Table II)	79·6	18·5	1·9	87·8	12·2
69 partial fraternities (Table III. Mat. age 30 and above)	75·8	20·5	3·7	83·0	17·0
62 partial fraternities (Table IV. Mat. age 35 and above)	70·3	24·8	4·9	77·1	22·9
41 partial fraternities (Table V. Mat. age 40 and above)	69·4	24·2	6·4	75·6	24·4

(All these quantities are given in the form of percentages.)

The values of A increase regularly as the strength of the environment increases. They may be supposed to be approaching asymptotically a value of about 25 per cent.

and, set out in this way, it is seen at once that there is a high incidence of miscarriages and infantile deaths just where there is a high incidence of mongols.

It now remains to decide what influence the consideration of undiagnosed individuals will have on the previously computed proportions

of affected children in the families and partial families as shown in Tables II, III, IV and V.

The results are set out in Table X, where it is assumed that the relative mortality (intra- and extra-uterine) of affected to normal is as *nine* is to *one*. It is to be observed that there is no need to make any correction of the number of undiagnosed cases such as that made for affected cases because the fraternities are in no way selected by the presence of undiagnosed individuals. Thus the ratio of u to x is equal to the ratio of the observed number of unaffected to the observed number of undiagnosed individuals. The effect of applying the formula already described is shown in a very marked increase of the estimated value for the familial incidence of mongolism.

4. MASS POPULATION INFERENCES IN RELATION TO THE INHERITANCE OF SUSCEPTIBILITY.

Before endeavouring to evaluate the significance of any ratio obtained in the study of genetic conditions affected by environment, the incidence of the trait in the general population must be known.

The effect of taking environmental agencies into consideration, as already described, is to raise the probable value of the proportions of persons affected in the fraternities studied. In order to obtain a numerical estimate for the true incidence of a genetic susceptibility we must obviously increase the observed frequency of the condition by a factor depending on the difference between the observed familial incidence and that calculated, after taking into consideration the environmental agencies.

In the case of mongolism we have found justification for raising the probable familial incidence of susceptible individuals from an observed 1·9 per cent. to a calculated value of over 20 per cent. Now there are, in two of the English counties where a fairly strict survey has been made of the incidence of mongolism, between 150 and 200 cases known to be living. The total population of these counties is 2,000,000. The absolute incidence of affected cases of nearly 1 per 10,000 must be multiplied at least by 10, to include susceptible persons as well as undiagnosed affected cases, giving a figure of 1/1000 for true incidence of the genetic condition.

Next must be considered the significance of susceptible parents who appear normal. Although manifestly affected persons may not function as parents (as in mongolism) these will only account for a small number of genetically affected persons.

It is easy to mistake a dominant type of inheritance for a recessive if a specific environment is necessary to make the genetic condition manifest. A satisfactory way of avoiding this difficulty is by the special study of the offspring of parents who themselves have been in danger of being affected by the specific environment. These families will usually be few and far between, but the task of finding them is not beyond hope. If both parents have been subjected to the environmental influence, are both normal and have affected children, inheritance by means of a single dominant gene substitution is ruled out altogether. Among the cases of mongolism I have collected, the parents of at least one patient were both born of elderly mothers, *i.e.* above 40 years. This fact makes single dominant determination unlikely.

Difficulty is met with in evaluating ratios of affected persons to normal when a common disease is studied, because it will not be known how many parents are of a genetic constitution likely to give high proportions of affected offspring. For instance, one has to be cautious in accepting a ratio of 25 per cent. as representing anything like what would be expected from a single recessive gene determination: the ratio should be nearer 26 per cent., if allowance were made for genetically affected parents, even with an incidence as low as 1 per 1000. In fact, generally speaking, the more the estimated familial incidence of a susceptible condition exceeds the observed familial incidence, the more we have to allow for the likelihood of parents being themselves genetically (but not manifestly) affected. The expected ratio of affected to normal on any given hypothesis will be raised accordingly.

The incidence of first cousin marriages is of the same importance in the study of inheritance of susceptibility as in other branches of genetics (10). In the case of mongolism it gives some information. Among over a hundred pairs of parents no first or second cousin marriages have been discovered. There is one example, however, of the child of a woman, who married her mother's half-brother, being affected. These observations make it unlikely that a single recessive gene determines susceptibility to mongolism[1].

There are other facts which make the recessive explanation of the disease unlikely. In the present series of 82 families there are two pairs of *patients* who are first cousins to each other and one pair of patients second cousins. In Fantham's (11) pedigree (though it is not very well

[1] But it must be admitted that, in raising the estimated frequency of the condition as high as 1/1000, a significant excess of first cousin marriages among the parents has been rendered improbable.

attested) the condition appeared in more than one member of the fraternity in three generations. Uncles and aunts of patients have sometimes been found to be affected. It is almost certain, therefore, that some kind of dominant heredity is responsible. The simplest explanation of the calculated ratio of affected children is to assume that the coincidence of two dominant genes is necessary to produce the condition, and that, if the analysis could be carried far enough, *e.g.* as far as the maternal age group 45 to 49 years, this ratio would exceed 25 per cent. To explain Fantham's pedigree on this assumption it would be necessary to add that these two genes may conceivably be located close together in the same chromosome.

Nevertheless it is not absolutely excluded that a *single* dominant gene may be responsible here. We are not certain that the environmental factor is continuously operative as maternal age increases. A possible cause, such as premature haemorrhage into the corpus luteum, might affect one pregnancy, and cease to operate subsequently. On the other hand, the values of A obtained in Table X may prove in the long run to be much too large should the families not be a representative sample, in which case the hypothesis of triple dominant determination would have to be considered. But it was not the purpose of this paper to come to a final conclusion on the aetiology of mongolism: the object was to demonstrate certain methods of tackling some difficult problems in human genetics. What stands out clearly is the need for the investigation of very much larger numbers of families when we are studying heredity, where environment has to be taken into account, than where it can be neglected. Details of each fraternity, such as the maternal age at all pregnancies, must be known, or the data are useless.

5. SUMMARY.

The effect of environment in the study of human genetics has been discussed, especially in relation to the observation of numerical ratios of affected persons to normal where the inheritance, not of a disease, but of the susceptibility to a disease is under consideration.

Methods of allowing for the effects of environments of graded intensity have been investigated.

The problem of selective mortality of affected individuals has been discussed, and a solution proposed.

The importance of the possibility of parents themselves being susceptible persons has been considered.

The methods which are described for attacking these problems are applied to data on the familial incidence of mongolian imbecility, which is assumed to have some hereditary basis. It is concluded that, if due allowance be made for environment, the proportion of susceptible individuals must be very much higher than is usually supposed in affected families.

It is concluded that the susceptibility to mongolism may possibly be determined by the inheritance of two dominant genes.

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