SOME GENETICAL PROBLEMS IN MENTAL DEFICIENCY.*

By L. S. PENROSE, M.A., M.D.

(From the Research Department, Royal Eastern Counties' Institution, Colchester.)

I. INTRODUCTION.

THE popular conception of mental defect is that it is a common abnormality of a kind fairly easy to understand and to study, and for whose ætiology simple rules can be laid down. Textbooks on general medicine usually dismiss the subject in a few paragraphs, and even those devoted to diseases of the mind rarely find room for more than one short chapter on mental defect.

Intellectual capacity is a quality which varies from one person to another, and mental defect can be defined as lack of intelligence so marked as to be outside normal limits. Since intelligence can be approximately measured—it is a fictitious quantity defined like the horse-power of a car or the tonnage of a ship—the lower limits of the normal can be agreed upon arbitrarily at a level convenient for any purpose which we have in hand. The great importance of intellectual defect is that it tends to make the affected person unfit to take full responsibility as a member of the society in which he lives. Thus, the limits of normal intelligence will vary according to the needs of the social group. The fact that the diagnosis is based upon social usefulness makes the subject of mental defect particularly puzzling from the medical point of view. A person who is normal in a rural district may be abnormal in a town. Moreover, to suggest that intellectual incapacity is the usual reason for certification under the English laws is to minimize the difficulties of the position, for patients can also be certified for lack of the usual moral responses. The social rejection of the individual is to a large extent unmindful of the cause of the incapacity. It matters little whether the disability is associated with congenital diplegia, early schizophrenia or mongolism: according to the law, the cases are just mentally defective. In fact, an enormous range of conditions which are entirely different, from the point of view of medical science, fall into the same category because of the social criterion. It is no wonder therefore that the topic of mental deficiency is the despair of physicians and psychiatrists alike. They dare not devote more space to its study in their textbooks; if they did so it would involve their writing preliminary chapters upon sociology and genetics.

When it fell to my lot to pursue an inquiry into the causes of mental deficiency, I had no conception at all of the magnitude and intricacy of the task or I should never have had the impudence to attempt it. I had been taught that

* Read at the Annual Meeting of the Royal Medico-Psychological Association at Ilkley, July 8, 1938.

https://doi.org/10.1192/bjp.84.352.693 Published online by Cambridge University Press

certain brain diseases and malformations gave rise to idiocy, and that many conditions studied by neurologists were to be found in association with mental impairment. But to say that certain changes in the brain were correlated in some cases with changes in the mind seemed to me only one side of the picture. When we know the morbid anatomy of a tubercular lung we know something about phthisis, but not very much: it is the identification of the bacillus and the observation of the reaction of the body to this organism which constitutes the real study of the disease. Now, since in a large number of cases of mental defect the condition is present at birth or in very early life, an early cause must be looked for, and attention must be focused upon the germ plasm. The causes of congenital diseases can only be said to be understood when the genetic units which underlie them can be specified, and the reaction of the organism as a whole to these genetic peculiarities observed.

The only effective way to study germ plasm in human beings is to investigate families, but opinions differ as to how this is to be done, and what interpretation is to be made of the data so obtained. In the wide range of literature available on the family investigation of mental defect, the first record of an outstanding success was Sjögren's (1) analysis of juvenile amaurotic family idiocy. Here a clinical investigation, supported by family history study, was interpreted in the light of the knowledge of the behaviour of the germ plasm obtained from animal genetics. A completely satisfactory explanation of the incidence of the condition was obtained. Sjögren (2, 3) has since investigated, by the same methods, some cases of imbecility without marked physical signs and also cases associated with cataract, and he has obtained less certain but nevertheless very suggestive results. It is, however, conclusively proved that the juvenile form of amaurotic family idiocy is a single Mendelian recessive character in man—a germinal defect of a kind very well known in animal and plant biology. The fact that, in such cases, mental defect appears at a comparatively late stage in development, and is acquired as a consequence of gross brain disease, has led some clinicians to classify the mental symptoms as secondary in spite of the hereditary causation. Even if the distinction between primary and secondary cases can be usefully made in the classification of other types of defect, it would seem that, in these circumstances, the antithesis is valueless.

II. Recessive Characters.

As a starting-point in a clinical and genetical study, one may be fairly safe in assuming the likelihood that if, in one disease giving rise to mental deficiency, a recessive gene is the ascertained cause, other diseases like it in this respect will be discovered. It will be well to mention here the signs by which recessive determination of rare hereditary traits in human populations can be detected. In human populations, if a Mendelian recessive character is rare, practically all individuals who exhibit the character have parents who do not exhibit the character though they carry the gene. In such families, a fraction, approaching

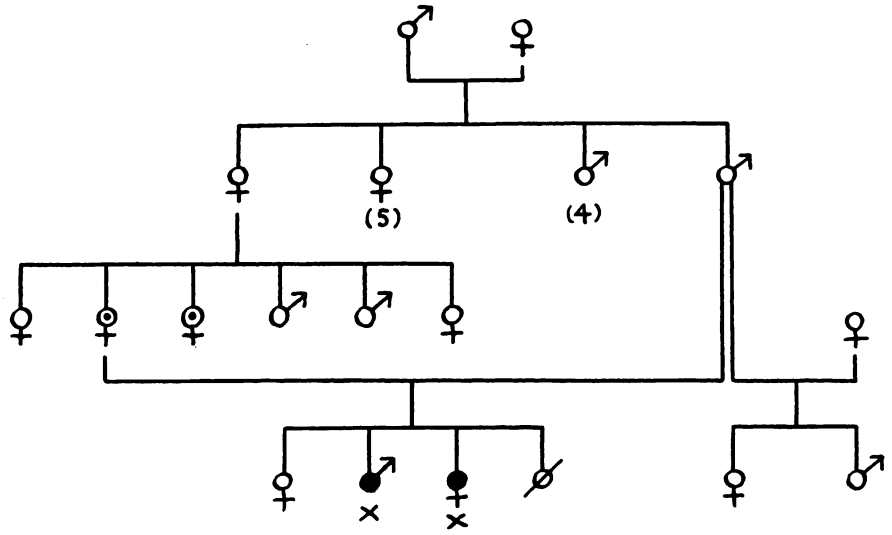
one quarter, of the children show the character, and they will be sharply distinguished thereby from the others. Furthermore, as Garrod (4) first pointed out in connection with alkaptonuria, the parents in these families will not infrequently be found to be consanguineous. It should be emphasized that these signs are typical of rare recessives, and that it is easier to identify a rare recessive trait than a common one.

That these criteria are all satisfied by amaurotic idiocy of the infantile type has been demonstrated recently by Slome (5) after a survey of the existing literature. Another disease in which the same signs are manifested unequivocally is what has been variously termed, imbecillitas phenylpyruvica, phenylpyruvic amentia, phenylpyruvic oligophrenia, phenylketonuria, or the syndrome of Fölling. In this condition, described first in Norway (6), the patients (imbeciles) excrete about a gramme a day of an abnormal metabolite. Normal relatives do not excrete the substance. One patient of this type, which I happened to identify, had a family history so perfectly in accord with the criteria for Mendelian recessivity in man that I had no hesitation whatever in ascribing this manner of causation to the disease. The view has been confirmed by the study of further cases in England and Scotland by my colleague Munro, and also in America by the investigations of Jervis (7).

Besides these certain recessives, there are a large number of probably recessive conditions which account for other rare types of imbeciles. The cases are uncertain inasmuch as one or other sign fails to be adequately exhibited in the families. There is, for example, the syndrome of Laurence, Moon and Biedl, but the segregation here, as in Griffiths's (8) case, is not perfect. Certain types of congenital diplegia are clearly determined recessively, but the difficulty remains of separating out one recessive diplegia from another. This is indeed a relevant problem, for familial diplegia is not always associated with mental defect. Some cases of cretinism, but certainly not all, appear to belong to the group of recessive defects responsible for mental impairment. An extremely interesting type with similar causation is the microcephalic dwarf, the Aztec type of Langdon-Down (9), with head significantly smaller than other aments of comparable grade. Barr (10), in his textbook, shows photographs of many brothers and sisters in one family who were affected. Several familial instances are known to me and, in one very interesting family (942)* (Fig. 1 and photographs), the parents of the microcephalics were uncle and niece. It would be rash, however, to assume that all such cases were due to the same single recessive gene, for the familial incidence does not approach, on the average, a high enough ratio. The study of recessive disease is a fruitful source of inquiry in the mentally deficient, and Munro has shown that it is also a valuable study in psychotics. The actual number of cases of mental defect,

* These numbers, which identify pedigree charts, are the serial numbers of cases summarized in Appendix 3 of "A Clinical and Genetic Study of 1280 Cases of Mental Defect" (*Sp. Rep. Ser. Med. Res. Counc.*, No. 229). The pedigrees are given here for demonstration purposes and are somewhat abbreviated.

however, which can be attributed with certainty to Mendelian recessive characters is small. According to our knowledge at the present time, it scarcely can exceed 5% of the inmates of our institutions. The position is therefore very



The fractions denote cephalic index, $\frac{\text{Biparietal cranial diameter in mm.}}{\text{Anteroposterior cranial diameter in mm.}}$

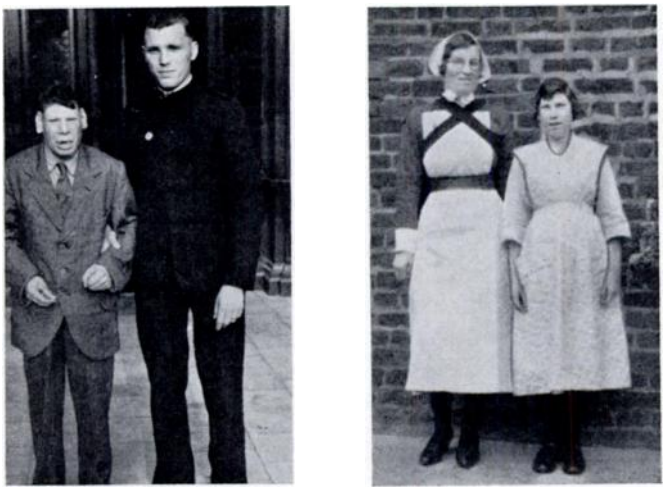
FIG. 1.—Pedigree of Case No. 942.

different from that envisaged by Goddard (11), who considered that all mental defect might be due to recessive Mendelian determination of a simple kind.

The influence of sex-linked recessive characters in the causation of mental impairment has been frequently stressed by investigators, notably by Rosanoff; (12), Macklin (13) and Sjögren (14). All these writers advance the theory that

https://doi.org/10.1192/bjp.84.352.693 Published online by Cambridge University Press

there is some prevalent sex-linked modifying factor which accounts for the preponderance of male defectives which is specially noticeable among imbeciles and idiots. The hypothesis is unlikely to be correct, because such a state of affairs is very rare in animal genetics. In a recent analysis of the data on which this theory is based, Csik and Mather (15) have shown that the postulation of sex-linked contributory factors is not justified. In my own institutional survey (16) more male than female idiots were examined, but the outcome of treating the sibship data on lines which resembled Mather's analysis of other



Photographs of the two adult imbeciles specified in Fig. 1, each with a normal person.

data did not support the view that sex-linked genes were of wide significance in the causation of mental impairment.

Nevertheless, undoubted examples of sex-linked inheritance have been described in man—such as hæmophilia and colour-blindness—and it is not unreasonable to suppose that some rare types of mental defect are thus caused. Recently, Roberts (17) has published an account of a family in which microphthalmia associated with mental defect is sex-linked ; that is to say, only males are affected but normal females may transit the disease. It is worth while also to mention that partial sex-linkage, in Haldane's (18) sense, should be looked for in pedigrees of mental defect associated with retinitis pigmentosa.

III. Dominant and Partially Dominant Characters.

The tests for a disease due to a single rare dominant gene in man are simple enough. Each affected person has one parent affected and the other parent normal : an affected person transmits the character to a proportion of his children which approaches one half, and there should be clear distinction

between normals and abnormals in families where the gene is transmitted. In animal genetics, dominant defects are very much less frequently found than those which are recessive. Even where the defect is alleged to be dominant the dominance is rarely complete ; that is to say, the offspring of two parents, both of whom are affected, contain a certain number of individuals who receive a double dose of the noxious gene and are thereby worse affected than the parents. Cockayne (19) and Levit (20) have pointed out that, in man, an unexpectedly large number of dominant, or partially dominant, pathological characters have been observed. In dominant diseases, however, the character usually shows much variation of intensity between one affected person and another even within the same family group. I know of no example of an inherited disease which is perfectly dominant in man, though physiological characters—like some of the blood agglutinogens—can have this property.

A dominant disease cannot be said to have been properly analysed until all the variations of its expression are known. Furthermore, it is possible to regard every person who suffers from a dominant disease as a potential carrier of a recessive, more severe, condition which has not yet been identified. Perhaps the most satisfactory human pedigree, which shows what the offspring of two parents with the same rare dominant defect would be like, was recorded by Nissen (21) ; in that family two consanguineous brachyphalangous parents produced a child with gross skeletal deformities. In the majority of cases in man, it is probable that the recessive state which corresponds to a known dominant disease is very severe and possibly lethal. The bearing of this question on the subject of mental deficiency, where cases of gross abnormality and deformity are not infrequently encountered, is fairly obvious and will be discussed later.

The identification of dominant factors which are the causes of specific types of mental defect has progressed only to a limited extent. Huntington's chorea, when it is of early onset, is occasionally associated with mental impairment of sufficient degree to warrant certification under the Mental Deficiency Acts. Certain types of acrocephaly, not yet fully understood, are dominant and may be found with mental deficiency. Two other dominant conditions are multiple neurofibromatosis and tuberose sclerosis. Both these diseases show great variability and are not always associated with mental defect. In the case of tuberose sclerosis, the mental impairment is sufficiently frequently observed for the syndrome of sebaceous adenoma, epilepsy, mental defect and brain tumours to have obtained clinical recognition by Sherlock (22) and to have been given the special name of "epiloia". None of these dominant diseases fulfil perfectly the criteria for single gene determination. The ratio of one half is seldom obtained in affected sibships because mild cases are not easy to detect. The age of onset of Huntington's chorea is variable and, as in epiloia, abortive forms of the disease are well known. Not infrequently the parents of affected cases do not themselves show signs of the disease. It is difficult, in some instances, to

know whether the assumption, that the parent who shows slight signs really has the disease in abortive form, is justifiable. Indeed if the patient is a very severe example of dominant defect and there is no other example in the family at all, then the hypothesis that the disease has arisen *de novo*, by gene mutation, is reasonable. Rare dominant defects are of particular interest in human genetics because it is possible, by means of extensive family history study, to estimate the mutation-rate of the gene. The results of Haldane's (23) analysis of hæmophilia and my own (24) of epiloia indicated that the mutation of genes, in relation to the length of the life-cycle, may be rather more frequent in men than in flies.

Although specific diseases with dominant inheritance are rare in the genetics of mental defect, it is at least probable that certain non-specific types of defect owe their origin to dominance of genetic factors which impair the intelligence. The feeble-minded and borderline cases quite often have at least one parent who is mentally dull or feeble-minded. The familial incidence of feeble-mindedness and of dullness is much higher also than that of defect of severe type. Despite the fact that, in mild mental defect, segregation of normal and abnormal individuals is usually imperfect, the simplest explanation of the relatively high familial incidence is that the genetic causal factors are dominant. Within the normal range of intelligence, it is a general rule that the mean mental ability of children is the same as that of the parents, and this holds also for families where mental subnormality is only slight. The genetical explanation of this effect, first proposed by Fisher (25), is that dominant genes cause variation in mental ability, and that the effects of these genes are additive. In its simplest form, the theory implies that, if each of two parents possess a gene which diminishes mental ratio by 10 points (i. e., the parental mental ratios are each 90), one child out of four will be normal (M.R. 100), two will be like the parents (M.R. 90), and one will receive from each parent a gene which diminishes intelligence by 10 points and will consequently have a mental ratio of 80.

It is logical to take one step farther in the application of this hypothesis, and to examine family histories for evidence of severe defect among the offspring of parents both of whom have subnormal mentality. In such cases it could be assumed that an idiot had received a factor detrimental to intelligence from each parent. Unfortunately, there is no certainty that the dominant gene which determines dullness in both parents is the same. The exceptional case, however, in which dull parents are consanguineous, is of special interest, for here the father and mother are likely to be similar in genetic constitution. In my survey of the patients of the Royal Eastern Counties' Institution, I found several families in which the parents of an idiot or an imbecile were themselves dull or feeble-minded, and in a few of these families there was parental consanguinity also. I quote here two families (91 and 46)* (Figs. 2 and 3) which show the effect clearly.

* See previous footnote.

Some of the early investigators in the field of heredity and mental disease paid great attention to the apparent deterioration of degenerate stocks. Mott (26), Tredgold (27) and Myerson (28) observed that, among the members of the families of idiots, mental diseases of several different kinds, as well as feeble-mindedness, were not infrequently found. The attribution of the idiocy in

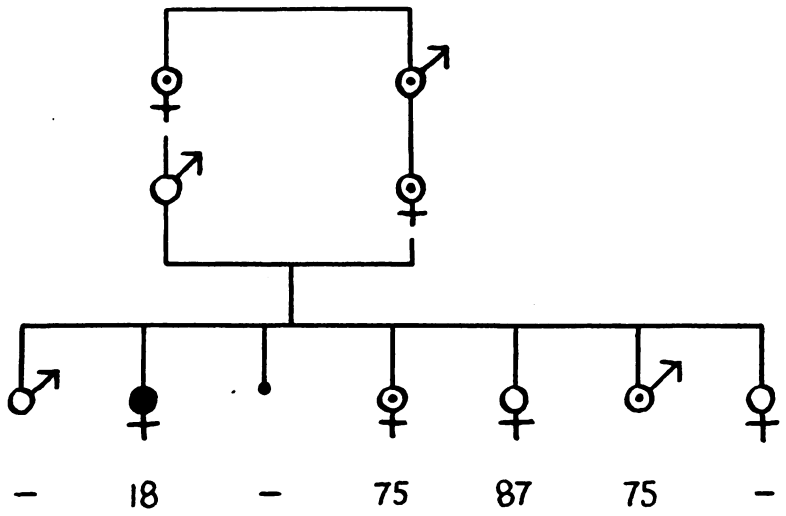


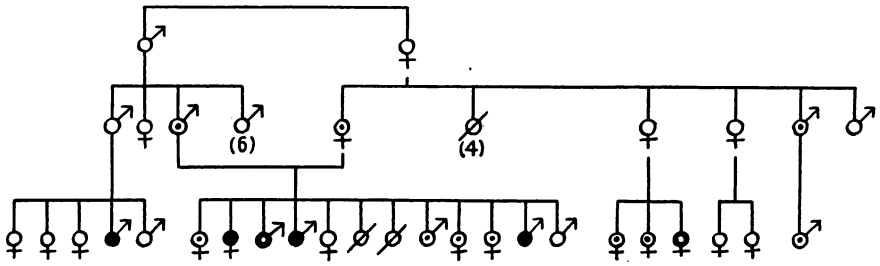
FIG. 2.—Pedigree of Case No. 91.

these families to progressive degeneracy was an inference based, I believe, upon incorrect assumptions concerning the nature of the processes of heredity, but there is no reason to doubt the correctness of the observations. A more likely explanation would appear to be that, in some of the families where degeneration of the stock has been postulated, the defective end result is due to a combination of partially dominant additive factors.

It would obviously be of the greatest practical importance to be able to identify the carriers (that is to say, the potential parents) of recessively determined defects. By starting from the recessive condition, it may be possible

to work backwards and identify much milder diseases which are really expressions of the same abnormality in the carrier. In the carrier these milder diseases would be most likely to appear as incompletely dominant conditions which would only be identified in a few relatives.

Sjögren (1) showed that insanity was slightly commoner among the parents of cases of amaurotic idiocy than in the general population. In the literature which describes families where the Laurence-Moon-Biedl syndrome has occurred, normal relatives (such as uncles and aunts) have sometimes been recorded who showed slight physical peculiarities which belong to the syndrome (obesity, polydactyly). I have myself observed a number of instances where cretinism



Intelligence within normal limits.

Dull.

Simpleton.

Idiot.

FIG. 3.—Pedigree of Case No. 46.

appears to be recessively determined; dysthyroidism of other kinds (for example, exophthalmic goitre) occurred among the relatives of these cases. In pedigrees of phenylketonurics, insanity with a mean age of onset of about 45 years and of characteristic type seems to be more frequent than might be expected in a random sample of the population. There is one difficulty which is met with in all such inquiries. If the disease appears strongly dominant in the parents, the offspring who receive a double dose of the gene may not survive. On the other hand, when the dominant condition is variable in type or late in onset and perhaps difficult to recognize as a hereditary disease at all, the recessively affected offspring with a double dose of the gene may survive and exhibit a well known congenital condition. That is to say, in families where there is but little modification or variation, the recessive type is likely to be unknown because it does not usually survive, and in families where there are many factors which modify the disease it is usually difficult to identify the carrier.

In examining the family histories of microcephalic dwarfs, I was surprised at the frequency of insanity with affective reaction among the relatives. I formed the opinion that these affective disorders were due to the presence of an irregularly dominant gene which caused imbecility or idiocy in the person who received a double dose. Some kinds of affective psychosis show very marked dominance, and it is a problem of great interest in psychiatry to discover what an individual would be like who inherited manic-depressive insanity from both parents. We could argue, by an analogy, that the result would be a severe form of idiocy which would possibly even be incompatible with survival.

IV. Environment and Heredity.

Any effective clinical and genetic method of psychiatric research must pay great attention to the environmental factors, for these are likely to be found to play a large part in the causation of mental diseases. In the sphere of mental defect, the scope of environmental influences to act as causes is limited on account of the early onset of the abnormality. Only in rare instances can an illness or an accident be shown to be a certain cause of impaired intelligence. Instances of this are encountered when there is deterioration after cerebral trauma or encephalitis in a child previously normal. In the majority of cases the identification of environmental causes has to be based upon indirect evidence. For instance, to demonstrate that congenital syphilis can be a cause of mental defect, the comparison of syphilitic children with their unaffected sibs is necessary. The study of unequally affected monovular twins is also relevant, and tends to show that congenital syphilis can at least account for a diminution of 20 to 30 intelligence quotient units. The recognition of special types of syphilitic disease—such as juvenile G.P.I.—is useful supporting evidence, for it shows that syphilis can certainly cause defect in some cases.

The significance of birth injury in mental deficiency is difficult to ascertain, because it can never be proved that the child would have been normal if he had not been injured at birth. It is, moreover, quite impossible in some instances to decide whether a child was injured at birth or not. According to Ehrenfest and Brander, prematurity is a predisposing cause of birth injury, and it can be demonstrated that premature infants are more likely to be mentally retarded than those who are born at full term. Unless premature children show signs of nervous diseases, such as hemiplegia, which could be attributed to cerebral trauma, the argument is not very cogent, for prematurity itself may be occasioned by fœtal abnormality. A possible line of investigation of the effects of birth injury would be to ascertain whether indeed idiots are more frequently first-born children than would be expected. Families in the general population in this country are diminishing in size, and to demonstrate a significant excess of first-born in a given group is becoming increasingly difficult. In my own data the mentally defective, particularly those of idiot grade, were first-born in the

family more often than was to be expected, but the excess of first-born idiots was not statistically significant ; a much larger series would be needed if the observation were to be substantiated. The implied assumption that the first-born child is more liable to injury at birth than those born later also needs confirmation.

The environment of the fœtus between the time of fertilization and birth can hardly be studied in any other way than by collecting data of large numbers of families, and comparing the circumstances of one pregnancy with those of another. Fortunately, data of this kind lend themselves readily to statistical analysis when parental age at the birth of each child is recorded. A number of developmental abnormalities which may cause mental impairment have something in common ætiologically. With one of these abnormalities, mongolism, mental defect is always present, and there is no doubt that the age of the mother at the time of the child's birth is a significant causal factor. The chance that a mongol child is born in a given family increases as the age of the mother increases : in fact, the probability is more than doubled every five years from the age of 25 onwards. The result is that mongol children are likely to be born last in the family, but there is no evidence that the order of birth, or the interval between births, is of causal significance, nor yet the age of the father. Sometimes cases of mild defect, or even normals, show one or more characters which form part of the syndrome of mongolism. In the cases of mental defect with incomplete mongolism which I have observed, the maternal age at the birth of the patient was significantly raised, though not to such a marked degree as with typical mongols.

Recent studies by Malpas (29) and by Murphy and Mazer (30) have focused attention on the whole group of abnormalities which are more liable to occur at the end of a family than at the beginning. Of these, anencephalus and congenital hydrocephalus are the commonest. Mental changes do not always accompany congenital hydrocephalus, but anencephalus would appear to be the most complete form of mental defect possible. It seems probable that, in the ætiology of both these conditions, as with mongolism, maternal age and not birth order is the important factor. Spina bifida also belongs to this group of developmental abnormalities, though it has rather less relevance to the study of mental defect than the others.

The genetic meaning of these phenomena seems likely to be elucidated by some discoveries which have been made in animal genetics. In the first place, Wright (31) has demonstrated that, in the guinea-pig, the age of the dam is a more important factor than genetic constitution of the offspring for the appearance of certain peculiarities : that is to say, certain strains of animals, although pure bred, still show variation, in coat colour and polydactyly, according to whether the dam is young or old. Wright showed also that the proportion of offspring who had the peculiarity was independent of birth order and age of sire. Secondly, in rabbits, Hammond (32) has found that does of a particular

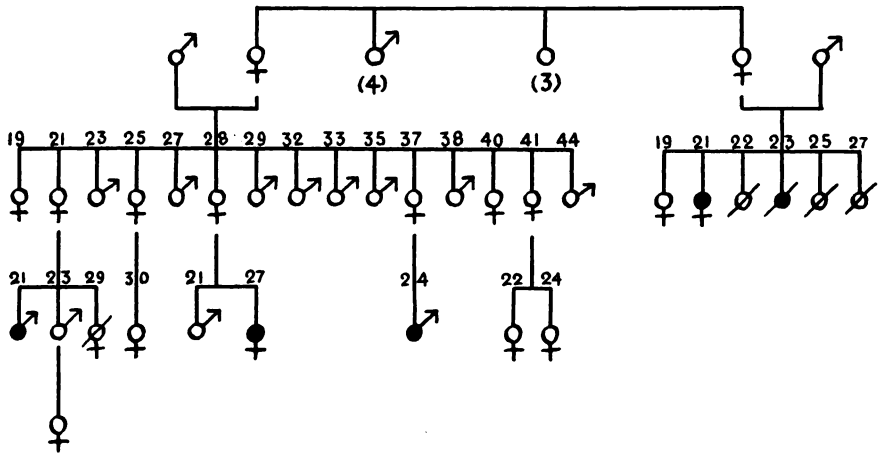
genetic constitution are especially liable to produce a high proportion of atrophic fœtuses; this maternal constitution is inherited as a Mendelian recessive character. Thirdly, genetic characters in flies have been identified which require specific environmental influences, such as special diet or temperature, in order that the character will be manifested in genotypical offspring.

Now, the occurrence of mongolism in man, like polydactyly in guinea-pigs, depends in the first instance upon maternal age. There is, secondly, a tendency for collaterals to be affected which, though slight, probably has significance. Two first cousins can both be mongols and, in such cases, it has usually been found that the mothers are sisters: this fact suggests that some women, like Hammond's rabbits, are by reason of hereditary constitution more likely to have abnormally developed children than others. Thirdly, the sharp segregation in familial cases, and the fact that binovular twins have often been described one of whom is affected and the other normal, may mean that there can be also a genetic difference in the children which predisposes one more than another to become a mongol, just as the gene for abnormal abdomen predisposes one fly more than another to be deformed. The causation of mongolism, I believe, may be threefold; it depends upon the age of the mother, the genetic constitution of the mother and possibly upon the genetic constitution of the child.

The familial incidence of mongolism has sometimes been doubted altogether, but I can quote here a remarkable pedigree (925)* (Fig. 4), discovered by my assistant, Miss Matthews, in which there were at least four cases of mongolism in two generations. Mongolism is so common (perhaps as common as 1 in 600 births) that two cases might be expected sometimes by pure chance to occur in one family; in this pedigree, however, the maternal age averaged about 26 years, and mongolism at this maternal age is rare (about 1 in 6000 births). The concentration of the four cases in this family group is therefore very unlikely to be fortuitous. Some of the mothers in this family may have been constitutionally liable to give birth to a mongol child at an earlier age than usual.

Cases of spina bifida are not always defective mentally, but their brothers and sisters may be, even if they have not the same physical abnormality. In one family group (116)* (Fig. 5), which was extensively investigated by Miss Newlyn, there were several cases of spina bifida and several of mental defect with epilepsy. The distribution of the abnormalities overlapped, and it seems reasonable to suppose, as a first approximation, that the same genetic factor was the predisposing cause of all the congenital abnormalities in the family group. The mean maternal age for the abnormal individuals was significantly greater than the mean maternal age for the normal brothers and sisters. The simplest explanation of this pedigree is that the disabilities are due to a partially dominant gene whose variable expression is connected with maternal age. It is of interest to record that, in the same district, there lived another family in which a case of

* See previous footnote.



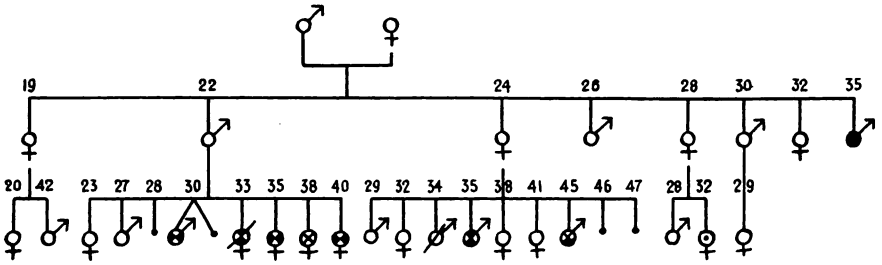
Mother's age at birth of child is indicated by unbracketed figures.

● Mongolism.

Died in infancy: probably Mongolism.

○ Normal.

FIG. 4.—Pedigree of Case No. 925.



Mother's age at birth of child is indicated by unbracketed figures.

● Spina bifida and epilepsy.

⊗ Spina bifida.

⊗ Mental defect and epilepsy.

⊗ Ectopion vesicæ.

⊗ Mental defect.

⊙ Goitre.

○ Normal.

FIG. 5.—Pedigree of Case No. 116.

https://doi.org/10.1192/bjp.84.352.693 Published online by Cambridge University Press

spina bifida occurred; the surname was the same but interrelationship could not be traced.

The human peculiarities, in the genetics of which maternal age plays a part, are not all pathological. Komai (33) showed that the mean maternal age at the births of binovular twins in Japan was 34 years; this mean age can be compared with that for Japanese single births, which is about 26 years. Also Dahlberg (34) and others have shown that there is much evidence in favour of the view that binovular twinning is hereditary.

V. Conclusion.

The few diseases in which hereditary mental defect has been clearly demarcated are found in idiots and imbeciles. Much less is known about the hereditary factors which underlie feeble-mindedness. Wildenskov (35), Lewis (36) and others have stated that feeble-mindedness is more hereditary than idiocy, but it is doubtful whether this view is a helpful one. I am inclined to believe that, in all grades of mental defect, heredity plays an approximately equal part, but that the degree of dominance of the hereditary factors is different in the various grades. Idiots and imbeciles are often recessively determined or due to fresh mutation, and are less obviously hereditary than simpletons who, like normals, owe their mental grade to the interaction of dominant additive factors.

Environmental influence may be the entire cause in comparatively rare cases, but is commonly a part cause of mental defect. The external circumstances indeed are likely to be even more important in mild cases than in severe cases, for their effects may make just the difference between certifiability and normality. The traditional question which demands whether a disease is primary or secondary in origin can rarely, in this subject, be answered with certainty. It seems that the only information which can be obtained will tell us how important environment and how important heredity is in a given type of case.

References.

(1) Sjögren, T.—" Die juvenile amaurotische Idiotie ", *Hereditas*, 1931, xiv.
(2) *Idem.—Acta psychiatrica et neurologica, Supplementum II*, Copenhagen, Levin & Munksgaard, 1932.
(3) *Idem.—Acta psychiatrica*, 1933, viii, p. 263.
(4) Garrod, A. E.—*Lancet*, 1902, ii, p. 1616.
(5) Slome, D.—*Journ. Genetics*, 1933, xxvii, p. 363.
(6) Fölling, A.—*Hoppe-Seyl. Z.*, 1934, ccxxvii, p. 169.
(7) Jervis, G. A.—*Arch. Neurol. and Psychiat.*, 1937, xxxviii, p. 944.
(8) Griffiths, B. M.—*Journ. Neur. and Psychopath.*, 1931, xii.
(9) Langdon-Down, J.—*Clinical Lectures and Reports, London Hospital*, 1866, iii, p. 259.
(10) Barr, M. W.—*Mental Defectives: Their History, Treatment and Training*, London, Rebman Ltd., 1904.
(11) Goddard, H. H.—*Feeble-mindedness, its Causes and Consequences*, New York, the Macmillan Co., 1914.
(12) Rosanoff, A. J., Handy, L. M., Rosanoff, I. A., and Inman-Kane, C. V.—*Journ. Nerv. and Ment. Dis.*, 1934, lxxx, p. 125.

(13) MACKLIN, M. T.—*Journ. Hered.*, 1936, xxvii, p. 97.
(14) SJÖGREN, T.—*Ann. Eugen.*, Camb., 1935, vi, p. 253.
(15) CSIK, L., and MATHER, K.—*Ibid.*, 1938, viii, p. 126.
(16) PENROSE, L. S.—*Sp. Rep. Ser. Med. Res. Counc.*, H. M. Stationery Office, London, 1938, No. 229.
(17) ROBERTS, J. A. F.—*Brit. Med. Journ.*, 1937, ii, p. 1213.
(18) HALDANE, J. B. S.—*Ann. Eugen.*, Camb., 1936, vii, p. 28.
(19) COCKAYNE, E. A.—*Inherited Abnormalities of the Skin and its Appendages*, Oxford University Press, 1933.
(20) LEVIT, S. G.—*C.R. Acad. Sci., U.S.S.R.*, 1935, ii, p. 499.
(21) NISSEN, K. I.—*Ann. Eugen.*, Camb., 1933, v, p. 281.
(22) SHERLOCK, E. B.—*The Feeble-minded*, London, Macmillan & Co., 1911.
(23) HALDANE, J. B. S.—*Journ. Genetics*, 1935, xxxi, p. 317.
(24) GUNTHER, M., and PENROSE, L. S.—*Ibid.*, 1935, xxxi, p. 413.
(25) FISHER, R. A.—*Trans. Roy. Soc. Edin.*, 1918, lii, p. 399.
(26) MOTT, F. W.—*Brit. Med. Journ.*, 1910, ii, p. 1013.
(27) TREDGOLD, A. F.—*A Text-book of Mental Deficiency*, London, Baillière, Tindall & Cox, 1937, sixth edition.
(28) MYERSON, A.—*The Inheritance of Mental Diseases*, Baltimore, Williams & Wilkins Co., 1925.
(29) MALPAS, P.—*Journ. Obst. and Gynæc.*, 1937, xliv, p. 434.
(30) MURPHY, D. P., and MAZER, M.—*Journ. Amer. Med. Assoc.*, 1935, cv, p. 849.
(31) WRIGHT, S., and CHASE, H. B.—*Genetics*, 1936, xxxi, p. 758.
(32) HAMMOND, J.—"The Inheritance of Fertility in the Rabbit", *Report of the VIIth Annual Rabbit Conference*, 1934, p. 557.
(33) KOMAI, T., and FUKUOKA, G.—"Studies on Japanese Twins", *Contributions to the Genetics of the Japanese Race*, Kyoto, 1937.
(34) DAHLBERG, G.—*Twin Births and Twins from a Hereditary Point of View*, Stockholm, Tidens Tryckeri, 1926.
(35) WILDENSKOV, H. O.—*Investigations into the Causes of Mental Deficiency*, Copenhagen, Levin & Munksgaard, 1934.
(36) LEWIS, E. O.—*Journ. Ment. Sci.*, 1933, lxxix, p. 298.