GENETICS IN PSYCHIATRY.

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GENERAL GENETICS.

WORKERS in psychiatric genetics are, with some notable exceptions, psychiatrists first and geneticists second. Neither their medical nor their psychiatric training equips them with an appreciation of scientific method, and their narrow specialization prevents them from keeping abreast of advances in the general field of animal genetics. As things are, this is an important source of weakness; for the general geneticist, whose science is in a much more advanced state, has accumulated facts and theories that have an immediate application in our special field. One has therefore to notice comprehensive reviews of the present position in genetics in relation to the theory of evolution which have recently been provided by Dobzhansky (1941) and Huxley (1942). In what follows the work of Huxley has chiefly been drawn upon, and it is intended to provide a brief summary of the most important of these ideas.

Huxley criticizes medical genetics for the tendency shown there to relate qualities in an absolute fashion to unit genes. "Actually, every character is dependent on a very large number (possibly all) of the genes in the hereditary constitution; but some of these genes exert marked differential effects on the visible appearance. Both rose- and single-comb fowls contain all the genes needed to build up a full-sized comb; but 'rose' build it up according to one growth-pattern, 'single' genes according to another. . . . Medical men have usually been obsessed with the implication of 'character-inheritance.' When the character has not appeared in orthodox and classical Mendelian fashion, they have tended to dismiss it with some such phrase as 'inheritance irregular,' whereas further analysis might have shown a perfectly normal *inheritance* of the gene concerned, but an irregular *expression* of the character, dependent on the genes with which it was associated and upon differences in environment. . . . To-day the notion of Mendelian characters has been entirely dropped."

Genes are thought of nowadays as exerting their influence by biochemical means and being concerned principally with the rates of processes. They themselves are subject to the same sort of influence. Timakov has detected in wild *Drosophila* a gene increasing mutation rates at least forty times, possibly to a higher level than that induced by X-rays. A gene may have a direct effect on two or more distinct processes and thereby on quite different characters, e.g. the white-eye allelomorphs in *Drosophila* also affect the shape of the spermatheca. A gene may affect a single process, but in many sites and conditions,

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e.g. Bonnevie's mouse gene which causes the exudation of blebs of fluid at a particular stage in embryonic development ; this causes widespread and phenotypically very different abnormalities, depending on the exact stage in development when the gene begins to exert its effect. A gene may produce a primary direct effect, and this in turn secondary effects. For instance, Grüneberg's rat gene causes hyperplasia of cartilage. The secondary effects of this are emphysema, hypertrophy of the right ventricle, blocked nostrils, incompletely occluded incisor teeth. Environment may mask or bring out the results of genetic differences: "vestigial" *Drosophila*, for instance, when grown under dry conditions, develops normally. The gene must be distinguished from its mode of expression. The gene is only altered by mutation, but its expression is the result of a balance between a very large number of factors, both genotypic and peristatic.

Large numbers of gene differences are extremely small, down to the limit of detectability. Multiple allelomorphs are very common, and up to a dozen or more are known for single loci. The differences between the effects of these are quantitative and may be very slight. It is probable that these genes of small effect are the main sources of the building blocks of evolution. They must be looked for wherever there is a continuous range of normal variability—for instance in psychiatry in the analysis of mental defect, temperamental instability, etc. Even genes of the classical type, which produce a gross qualitative change, will be subject in their expression to the influence of these genes of small effect, which are here called modifiers. The influence of these genes may be expected to show itself in, for instance, determining the age of onset of schizophrenia, and in causing differences in the clinical picture when schizophrenia is exhibited in a pyknic or a leptosome habitus. Evolution has probably proceeded by accumulating modifiers to damp down the undesirable effects of genes whose main effects are advantageous.

The distribution of genes within a given population is an important subject of research. The very large numbers of recessive genes which are carried in heterozygotic form by most animal populations are an important source of variability, without which evolution could not occur. The larger the size of the interbreeding population, the greater the potential genetic variability. In small populations the Sewall Wright phenomenon of drift can be observed, i.e. the chance accumulation or extinction of mutations, with resulting decrease in variability. Large populations can carry slightly deleterious mutations with reasonable frequency, especially when recessive, having thereby a reservoir of potential evolutionary change. For if such a recessive gene has an advantageous effect under changed circumstances, the accumulation of modifiers will with time suppress its deleterious qualities, and even shift its effect from recessivity towards dominance.

The importance of these notions for an understanding of the problems of psychiatric genetics will become abundantly clear in the following pages.

The Theory of Psychiatric Genetics.

Penrose (1942*a*) points out that the effect of natural selection is rapidly to eliminate harmful dominant mutations which produce their effect before or in

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the reproductive period. They can be kept going only by a considerable rate of fresh mutation (e.g. epiloia). Recessive conditions, and dominant ones which produce their disadvantageous effect after the reproductive period, are less susceptible. The accumulation of modifiers will tend to postpone the manifestation of dominant mutations till later in life, and as the reproductive period is longer in the male than in the female, the degree of postponement will tend to be greater in the male. Penrose quotes evidence to show that this is so in the case of Huntington's chorea and manic-depressive psychoses. Penrose suggests also that the disease is more frequently recognized in females, and may run a milder course in males. It is, however, difficult to see, if this is the case, how it could be an effect of natural selection. Penrose develops the argument to show that in the case of recessive conditions the converse should be true, and gives some evidence that in the case of schizophrenia and mental defect it actually holds. Again, however, it is not made clear why this effect should be an expected one. Either the reviewer has not rightly understood the argument, or a *non sequitur* has been allowed to creep in. The basic notion is that dominant abnormalities are exposed to the action of natural selection, whereas recessive conditions are relatively sheltered. From this it follows that certain differences between the sexes may be expected in the case of dominant conditions, which will probably not be seen in recessive ones, but not that the latter will show the converse of the phenomena observed in the former.

Penrose (1942*b*) has made another interesting contribution to general theory. It has been observed that when two relatives are both affected by some form of mental disorder, the relationship is more often between two males or two females than between a male and a female. From the publications of Mott and Myerson and his own material Penrose collects data about 2,363 such relationships, and finds a correlation coefficient of approximately + 0·11, which is certainly significant. He attempts to explain these findings by the following hypothesis. Sex is determined not only by the XY chromosomes, but also by the autosomes. Sexual differentiation is not simply into male and female, but is a bimodal distribution showing overlapping. American psychological test results have shown that some females are more male mentally than are some males. A gene which tends to produce masculinity will not produce noticeable effects in a person already constitutionally male, but will have an observable effect in the female. The converse will be true of genes predisposing to femininity in the male sex. These genes occurring in families will therefore tend to show a male-male and a female-female type of coupling. If any of them also predispose to mental disorders, these mental disorders will also tend to show the same type of coupling in family histories. The argument does not seem to be sound. Given that a gene causing a feminine attitude of mind in the male will tend to show a male-male type of coupling in family histories, it does not follow that any associated effects in producing mental disorder will show the same type of coupling. Only if the hypothetical feminine gene tended to upset the balance of the male mind and not that of the female would such an effect be observed, and there is no reason for believing this to be so. Alternatively it would be necessary for these accessory sex genes,

hypothetically also capable of producing mental disorder, to have at times the effect of actually altering the manifest sex of the individual. A simpler explanation of Penrose's interesting finding would be as follows: We know that the manifestation rate and the form of expression of genes are influenced by a great number of other factors than the gene itself, genetic, biochemical, and more strictly environmental. It is then only necessary to suppose that some of these factors are more likely to be the same for persons of the same sex than for persons of opposite sex.

Interesting work, fundamentally concerned with the same idea, has been done by Lang (1939) on male homosexuals. Arguing that imbalance between the sex chromosomes and the autosomes can, as has been demonstrated by Goldschmidt in *Lymantria*, produce reversal of the manifest sex in man, and that persons of reversed sex are more likely to be found among homosexuals than among normal individuals, he calculates that if one were to examine the sex distribution in the sibs of male homosexuals one would expect to find an excess of males. With the co-operation of police officials, he was able to obtain data about the sex of the sibs, living and dead, of 1,517 male homosexuals. These consisted of 2,534 males and 2,034 females, being 124·6 males to 100 females, a ratio that differs from the normal expectation of 105 : 100 by a margin that is highly significant statistically. A control investigation of the sibs of a solely male group of propositi of comparable size showed no such shift. Taking only the older homosexuals, who might be expected to be a more highly constitutional type, the male shift of the ratio was still more marked. Data are also provided about the half-sibs, and twins, also significant. Lang suggests that there may be, apart from the possible genetic basis, a hormonal interference in utero, as occurs with the free-martin. He points out that further research is needed, and suggests particularly the investigation of female homosexuals and of the frequencies of colour-blindness in both types of homosexual.

An observation of minor theoretical interest has been made by Idelberger (1939). According to him, the incidence of club-foot, wherever reported, is always 2 males to 1 female. This would be inexplicable by any normal form of Mendelian inheritance, and he suggests that manifestation is controlled by sex-linked modifiers.

Population Problems.

The frequency and distribution of genetic differences in human communities have been discussed by Dahlberg (1941). He particularly directs his attention to disturbance of amphimixis, or randomness of marriage and fertility, by the isolate effect. The general population is made up of a number of isolates or inbreeding communities. The limits of these, which are seldom sharply defined, are of geographical, social, occupational, religious and other kinds. The smaller the isolate, the more frequent is homozygosity. Isolate boundaries are now breaking up. The frequency of cousin marriage decreased in Bavaria from 0·87 per cent. in 1876–80 to 0·20 per cent. in 1926–33. This would suggest that the size of isolates is on the average double, perhaps treble that of fifty years ago. There should be a corresponding decrease in the incidence of recessive abnormalities, e.g. idiocy, impossible to measure in fact owing

to poor registration. One should also observe the wider manifestation of the effects of dominant genes, perhaps indicated by an increase of 9 cm. in the average stature in Sweden in the past 100 years. Dahlberg also considers the effects of selection, particularly on recessive conditions. Once the frequency of recessive conditions has reached a lowest limiting level, selection against the homozygote will be ineffective in reducing the frequency of the gene. Dahlberg hopes that rare qualities, such as the capacity for independent thinking, may prove to be dependent on recessive genes ; for then they would be inextinguishable, no matter how ruthless the effort to exterminate such individuals.

Further theoretical mathematical work on the statistical methods to be employed in the investigation of inbreeding have been carried out by Haldane and Moshinsky (1939). The authors have specially dealt with cousin marriage. Such basic theoretical work is very necessary for the effective application of practical research. It would be most desirable that comparable work should be done on the mathematics of assortative mating, as is shown by the inadequacies of Koller's work, to be discussed later.

Osborn (1939) has examined the fertility of graduates of Princeton University with samples taken over 30 years. The group has a low fertility, below replacement rate, but it increased slightly over the 30 years. Within the group there was some association between success, both at college and later, and fertility. A parallel investigation of the association of fertility with intelligence has been carried out with care on a large group by Fraser Roberts (1939). A sample of 3,400 children was submitted to intelligence tests. The association between intelligence and number of living sibs provided a correlation coefficient of — 0·224. Intelligence fell off evenly and steadily as the number of sibs increased, and vice versa. This has confirmed similar findings in the U.S.A. A more detailed examination of the highest 4 per cent., median 4 per cent., and lowest 8 per cent., rated by intelligence, showed that the more intelligent families were complete, whereas a large proportion of the families of lowest intelligence were incomplete. The correlation coefficient is therefore an underestimate. Roberts also showed that intelligent people of the lowest social class were just as infertile as persons of comparable intelligence in higher classes. The restricted fertility of the intelligent is, presumably, deliberate, though Roberts does not say so.

Brugger (1939*b*) has examined the debated topic of the relation between migration and intelligence. It is often asserted that in rural populations the more intelligent tend to migrate to towns and places of greater opportunity. In Switzerland Brugger obtained, by a follow-up of 1,700 rural ex-school-children of the years 1895 to 1920, no evidence of any preferential migration of this kind. He points out, however, that Switzerland is in a rather special position, as the opportunities and facilities of country life differed little from those of towns. There were also no observable differences when emigration abroad or overseas was considered.

Grobig (1939*a*, *b*) has investigated the frequency of the more important psychiatric abnormalities in the children, sibs, nephews, and nieces of a superior population group (works foremen and their wives), and has found their incidence to be below average expectations.

Literature, Reviews, Etc.

General reviews of recent advances and modern theories have been provided by Bleuler (1939), Brugger (1939), Hurst (1940), Kallmann (1941*b*), and Stumpfl (1939*a*). Bleuler deals with the endogenous psychoses and epilepsy, Brugger with mental defect, Stumpfl with psychopathic personality. The greater part of Hurst's article is concerned with Kallmann's work on the genetics of schizophrenia; he particularly discusses Kallmann's theory that the anatomical substratum of the predisposition to schizophrenia is an inherited weakness of the reticulo-endothelial system. Kallmann's review is intended for a non-specialist medical audience. He emphasizes his view that schizophrenia and manic-depressive syndromes must be considered distinct clinical entities based on independent and specific autosomal hereditary factors. With a strict psychiatric definition of the two conditions they are not found to occur together in the same families.

Discussions of points of general or particular research interest have been provided by Conrad (1939), Davidenkov (1940), Essen-Möller (1940), Panse (1939), Schulz (1939*a*), Slater (1939). The papers by Schulz and Slater are concerned with the statistical technique of twin investigation. Conrad emphasizes the quantitative aspects of gene activity, and attempts to familiarize the psychiatrist with other current genetic concepts. Davidenkov's paper is of more neurological than psychiatric interest. He discusses the problems raised by the observation that clinically identical conditions may follow different modes of inheritance in different families, or may show different degrees of penetrance in different families or in the same family in different generations. He deals with the problems of gene interaction, of minor anomalies and organ inferiorities in the families of persons showing an inheritable disease chiefly incident on those organs (e.g. the frequency of pes cavus in the families of subjects of Friedreich's ataxia), etc. Essen-Möller, in a discussion designed for a general medical audience, relates modern genetic theory to empirical advances in psychiatric genetics. He discusses the importance of the time of incidence, in the course of the individual's development, of the effects of a mutant gene, and suggests that the association of an asthenic physique with early onset, and of an athletic or pyknic physique with a late onset of schizophrenia, may be due to the biological effects of the schizophrenic gene itself. Panse pursues somewhat similar notions, and emphasizes the importance of distinguishing the abnormal gene from its phenotypic effects. The purpose of genetic research is rather to discover what is inherited than to force observed familial differences into a theoretical scheme.

Meggendorfer (1939) has reviewed the subject of alcoholic blastophthoria. It is well known that the application of X-rays or of any polarizing ray above 3022Å will increase mutation rate in the germ cells; and there is evidence that the same effect can be produced by other agents, including chemical ones. Forel suggested many years ago that the germ cells of the alcoholic might be damaged in this way. Blum observed such an effect in mice, but the abnormalities caused did not persist into the second generation. Family investigations in man have given equivocal results. Panse found no difference in the children

of alcoholics born before and after the time the addiction of the parent began. Meggendorfer concludes that some effect of alcoholic addiction on the mutation rate is probable. Jahnel (1939), on the other hand, concludes, after a discussion of the relevant literature, that syphilis has no such effect.

Mental Defect.

The genetics of mental defect have been greatly clarified, largely as the result of work in England and America. Research workers of outstanding ability in Germany and Switzerland are still puzzling themselves with out-of-date problems, as a result of their neglect of the accurate quantitative methods of measuring intelligence now available. The highly developed tests of intelligence that we use here and in the U.S.A. seem to be unknown on the Continent. Our present knowledge of the genetics of mental defect has been excellently summarized by Fraser Roberts (1941*b*). The intelligence of the normal and healthy human individual is determined by a very large number of genes of small quantitative effect. Where many genes of positive effect are present intelligence will be high; where the majority are of negative effect intelligence will be low. The frequencies of persons of high, average, and low intelligence in the general population are such as is required by this theory, i.e. they form a curve of normal distribution. In this respect intelligence is comparable with stature. There are, however, too many persons of low intelligence (as of low stature) to be accounted for by normal variation. A rough dividing line can be drawn between the normal and the morbid, at about I.Q. 45. Feeble-minded persons are to be considered abnormal only against the background of our society. The frequency of mental dwarfs is not high, being in school-children about 4 per 1,000. Rare specific genes, productive of very low grades of mental defect, must be very numerous; for gross mental deficiency means only a grossly impaired central nervous system, which may be caused in a great variety of ways. The specific forms now sifted out—phenyl-ketonuria, amaurotic idiocy, etc.—together do not account for 1 per cent. of low-grade deficiency. Most of these genes produce other effects than on the central nervous system; and conversely genes known for other effects, e.g. that of albinism, also produce changes in the C.N.S. in a proportion of cases.

Fraser Roberts (1940, 1941*a*) has supported this general theory with confirmatory evidence. A sample of 608 children taken from a larger group gave a sib-sib correlation in point of intelligence measurements of $+0{\cdot}535$. He concludes that the correlation coefficient must be taken to exceed $+0{\cdot}5$ (the amount demanded by the multifactorial theory) by an amount which is probably provided by a significant correlation between the intelligence of the two parents. It would be very desirable to have an actual measurement of this correlation, and further evidence of value could be obtained from the correlations provided by intelligence measurements in other degrees of relatives. Nevertheless the evidence already obtained is such as to make it practically certain that the multifactorial theory is correct.

This being so, one cannot give the attention it would otherwise deserve to

the painstaking and thorough work of Brugger (1940, 1941) and Juda (1939*a*, *b*, *c*). Brugger supports the genetic uniformity of clinically uncomplicated mental defect, and provides evidence for this by collating his own family investigations with those of other Continental workers, to give tables of frequencies of different degrees of defect among the various relatives of defectives of different grades. Regarded with insight, his tables, arranged purely qualitatively, show the clearest indications of quantitative relationships. Juda (1939*a*, *c*) has investigated 392 twin pairs from 485 twin births found in 18,183 ex-special school-children. Endogenous types of defect showed 100 per cent. concordance in the uniovular pairs. The frequency of twinning, 2·86 per cent., is the highest yet recorded in any family investigation, exceeding the high frequency found by Conrad in epileptics. Binovular twins were markedly in excess. Juda interprets this as a chance result, but the figures are significant. Prematurity and birth anomalies were more than averagely frequent. She discusses the exogenous causes of defect in detail, parental occupation and fertility, the frequency of illegitimacy, of socially inferior homes, of psychopathy and psychosis in the propositi. The frequency of schizophrenia was not raised, but that of epilepsy was. She supports Smith's view that the majority of cases of defect with neurological abnormalities are also of genetic causation. The very rich and important twin material is presented in summarized form case by case. In another paper (1939*b*) Juda considers the genetics of the mildest degrees of defect, and concludes that these cases are only in part of genetic causation. Without quantitative measurement it is impossible to be certain of the very slightest degrees of defect, and this work is of little value.

Damon (1941) has investigated the physical correlates of mental defect. His work, which is done with great care and thoroughness, both anthropometrically and statistically, shows that morons differ significantly from normals in a number of bodily measurements, and show in general greater variability, smaller size, relative preponderance of linear development, low sloping forehead, prognathism, receding chin; narrow temporals, marked asymmetry, thick lips, weak hair development. Dayton and Truden (1940) present statistical data on maternal age at birth of normal and defective behaviour problem children in 23,422 families. They find in the sub-average, but especially in the imbeciles, an excessive representation of the 35–49 age-group, which is statistically assured. An interesting note on geographical differences in the inheritance of defect is reported provisionally by Langner (1939). In Upper Silesia he found in the families of defectives a lower incidence of defect and an excess of male defectives, whereas in Lower Silesia the sexes were evenly represented. The two populations differ in other psychiatric and biological properties. Langner suggests that sex-linked factors are present in Upper Silesia which are lacking in Lower Silesia. Criticism must await a larger material and more detailed accounts than are presented in this summarized paper.

Other contributions to the study of ordinary forms of mental defect are of less importance. The work of Berry (1939) is of greater importance to eugenics than to genetics. Duff and Dinger (1941) found non-significant differences in

the incidence of consanguinity between certain clinical groups. Keiser and Halperin (1939) give a preliminary account of a sib investigation in which the data are dealt with by the new technique of analysis of variance. Hopwood, Kirk and Keiser (1941) report some hard work done for nothing, their data being presented in a way which is useless for comparison. Hecker (1939) suggests that idiots in whom destructiveness is a marked trait are more likely to show exogenous causation. Hell (1939*a*) finds, from an examination of 174 defective and control twin pairs, that late development of walking, speech and sphincter control are more characteristic of exogenous than endogenous defect. In another study (1939*b*), she finds no great differences between normal and defective twins in frequency of prematurity, birth anomalies, etc. On this issue the work of Juda is probably to be preferred. Mäurer (1939) reports a large number of air encephalograms, and finds them useful in distinguishing between endogenous and exogenous defect. Southwick (1939) followed up 488 children of institutionalized defectives, and found that their intelligence values could be fitted to a normal curve with mode at I.Q. 60–69 above that of their institutionalized parents (I.Q. 55)—an expected regression towards the norm. His findings support the multifactorial theory. Wardell (1941) gives a valueless account of a family of defectives extending into six generations and 300 members. Penrose (1939*a*) has given a useful table of expectations of defect when the mental grade of a parent or sib is known, and (1939*b*) has discussed in a stimulating way existing and possible future lines of research into the genetics of defect.

A number of reports are to hand on specific forms of defect. Jervis (1939) describes in full 125 families containing 200 cases of phenylpyruvic oligophrenia—a very large collection of a very rare syndrome. The statistical analysis is exhaustive, sufficiently so to provide a useful exercise book on statistical methods in psychiatry. Simple recessive inheritance is proven. No association with other abnormalities is found. Schröder (1939*a*) has reported on 49 mongol sibships. Ross, Hawke and Brown (1941) report four cases of gargoylism in two sibships. Halperin and Curtis (1942*b*) report one case, the only abnormal in a sibship of three; they discuss families previously reported, and conclude that the inheritance of gargoylism is simple recessive. Jervis, Roizin and English (1942) describe the clinical and pathological findings in a case of juvenile amaurotic idiocy. Jervis (1941) has also described six cases in a sibship of fifteen; he discusses the inheritance, which Sjögren has found to be of simple recessive type. Whitnall and Norman (1940) report in detail a case of microphthalmia; the family history, previously reported by Fraser Roberts, showed sex-linked inheritance through four generations and 14 patients. Kallmann, Barrera and Metzger (1940) also report a sibship containing four cases of microphthalmia, two of them being the first pair of uniovular twins reported. Inheritance here was of the simple recessive type. Oliver (1940) has reported an unusual family showing recessive polydactyly associated with mental defect. Polydactyly is usually dominant, and not so associated. Halperin and Curtis (1942*a*) report a case of anhidrotic ectodermal dysplasia associated with mental deficiency. Most reported cases have shown sex-linked recessive inheritance, and the association with mental defect has not

been previously noted. In this family inheritance was of the usual type. The authors suggest that the ectodermal dysplasia in their case had affected also the development of the nervous system, and that the defect was thereby a direct result of the syndrome. It might, however, quite easily be merely coincidental. Illing (1939) has reported seven cases of tuberose sclerosis, two of whom were sibs. The incidence of epilepsy, mental defect, minor skin abnormalities, etc., in the families are discussed. In his discussion of the genetics of this disease the author shows himself ignorant of Penrose's work. Ferriman (1941) has discussed the genetics of oxycephaly and acrocephalo-syndactyly; he concludes that inheritance is dominant, and that the association of syndactyly with oxycephaly is either due to the action of modifying genes or to the genes responsible being allelomorphs. Thums (1939) has gathered the large number of 90 pairs of twins, one or more of whom showed Little's disease. Of the 13 uniovular pairs 1 was concordant, 3 partially concordant, 9 discordant. Of the 33 binovular pairs, 2 were concordant and 2 partially concordant. He concludes that other factors than heredity must play a decisive role.

SCHIZOPHRENIA.

Probably the most important contribution to the genetics of schizophrenia is a statistical paper by Koller (1939). He makes use of the large family material provided by the researches of Kallmann. The finding which proves of most critical importance is Kallmann's observation that the incidence of schizophrenia is greater in the children of schizophrenics than in their sibs. This proves difficult to reconcile with any ordinary mode of inheritance, particularly with recessive inheritance. No adequate account or criticism of Koller's paper can be given here. His method consists in taking one or two of the empirically observed frequencies as given, and on the basis of various theories of inheritance predicting further rates of incidence, which are then checked against observation. The method is far from rigid and lacks elegance. Nevertheless, it is shown fairly convincingly that on the theory of recessive inheritance it is impossible to explain Kallmann's findings without a quite unlikely intensity of in-breeding among schizophrenic gene carriers, which is negatived by Leistenschneider's investigation into the consorts of schizophrenics. A theory of simple dominance with only a slight degree of assortative mating and with a plausible value for the manifestation rate fits empirical findings fairly well. Essen-Möller (1940) also supports the theory of dominance. He mentions, however, a suggestion of Strömgren's that the ratio of incidence in children to incidence in sibs, which is so inconveniently high for the theory of recessivity, might be explained by a higher manifestation rate in the children. The argument is not given in detail, and there is no reference to the original. Further recent support to the theory of dominance has been provided by the statistical demonstration by Schulz that at least 60–66 per cent. of all schizophrenic matings must be regarded as potentially productive of schizophrenic children.

Kallmann himself supports the theory of recessivity, and Kallmann and Barrera (1942) have recently restated it, unfortunately without mention of the

work referred to above. They postulate a wide variation in the expressivity of the schizophrenic gene, which is subject to modification by a number of accessory genes, quantitative in their action. They have interesting remarks to make on schizophrenic twins, of which they have now collected 400. A brief account of the same material has also been given by Kallmann (1941*a*). Of the dizygotic twins, 12·5 per cent. are schizophrenic, 14·4 per cent. schizoid personalities. Of the monozygotic twins 81·7 per cent. are schizophrenic, 10·5 per cent. schizoid personalities. They are analysing these twins by Sheldon's technique, which provides indices of the relative preponderance of asthenic, athletic and pyknic components of bodily habitus. Analysis of 412 schizophrenic non-twins, for which the figures are given, shows a negative association of the athletic component and a positive association of the asthenic component with degree of deterioration.

Contributions of importance to theory have also been made by Elsässer and Schulz in provisional form. Elsässer (1939) examined the children of matings in which both parents were psychotic. The frequency of psychosis in the children was: In 10 schizophrenia × schizophrenia matings, 50 per cent.; in 2 manic-depressive × manic-depressive matings, 65 per cent.; in 6 schizophrenia × manic-depressive matings, 40 per cent.; in 10 atypical matings, 47 per cent. The author concludes that atypical autochthonous psychoses are to be regarded as endogenous. Schulz (1939) presents briefly the findings in 386 sibships where there was psychotic tainting on both sides. Where both parents were schizophrenic, the frequency of schizophrenia in the children was 31 per cent., manic-depressive psychosis, 10 per cent.; where one was schizophrenic, the other manic-depressive, corresponding percentages were 14 and 16, and where both were manic-depressive, 15 and 20. Schulz also presents other tables, e.g. where one parent was psychotic, the other having a psychotic sib, etc. The results, though very interesting, are based on too small absolute numbers for any very definite conclusions to be drawn. Schulz considers that they indicate that endogenous psychoses depend on dominant factors. For instance, where both parents themselves non-psychotic had psychotic sibs, one would expect on the theory of recessivity a much higher frequency of psychosis than among the ordinary nephews and nieces of persons suffering from endogenous psychoses. Instead, the frequencies are much the same. Schulz thinks that pure and simple dominance is as readily excluded as simple recessivity; for if simple dominance held one would not expect an incidence of schizophrenia in the children of two schizophrenics to be more than half as great again as in the children of one schizophrenic, whereas it seems to be twice or three times as great. This may be admitted; but when the influence of the genotypic milieu has to be taken into account, the theory of a single specific dominant gene remains a possibility. In a further treatment of the same subject, not accessible to the reviewer, Schulz (1940) concludes that the results of matings between schizophrenics and manic-depressives support the possibility that there is a genetic factor common to both.

A valuable collection of 92 schizophrenic sibs contained in 38 sibships has been reported by Zehnder. The detail in which the cases are presented is

particularly welcome, as further research on the published material will be possible. She has found many different types of end-state in the same sibship, and concludes that heredity determines only the presence or absence of schizophrenia, but not its picture and course. A more adequate statistical examination, which the size and comprehensiveness of her material would make well worth while, would probably not confirm this view.

Other contributions to the genetics of schizophrenia are of minor interest. Wespi (1941) has described in great detail a pair of schizophrenic uniovular twins, and relates differences in clinical picture to slight differences in temperament. Rainey and Carson (1941) have described without comment a family showing paranoid schizophrenic psychoses through three generations. Meyer (1942) has reported a family of 59 individuals extending over four generations, in which both mirror movements, with a dominant type of inheritance, and schizophrenia occurred. There was no sign of any connection between the two conditions. Kant (1942) has investigated the family histories of 100 schizophrenics, of whom 50 made good recoveries, confirmed after four years, and 50 who deteriorated. The investigation was interestingly designed but inadequately carried out, the principal objection being that the table provided is in the form of "number of patients with familial abnormality." The material was worth a more extended analysis giving the incidence of abnormalities in the relatives arranged in age-groups. Kant observes a higher incidence of familial tainting in the recovered than in the deteriorated group, the bulk of the tainting in the former being manic-depressive, in the latter schizophrenic. One suspects a Meyerian looseness of diagnosis. If reliable, the finding would support the ideas of Schulz, mentioned above.

Kallmann, Barrera, Hoch and Kelly (1941) have examined the possible connection of schizophrenia and mental defect, with the aid of a large series of schizophrenic twins. It is impossible to do justice to this interesting paper in the space available. In 365 pairs of schizophrenic or mentally defective twins, no single pair could be found where one member was schizophrenic only, the other mentally defective only. The relations throughout were such as one would expect if the association were purely accidental.

Harrasser (1939*a*, *b*) has provided some information about racial types in schizophrenia, with correlations between race, physical constitution, and form of illness. The figures are in the form of percentages, and neither the methods by which they are obtained nor the criteria on which racial and constitutional types are differentiated are made clear. Investigations of race are more likely to be profitable in the U.S.A. than in Germany. Wrexberg (1941) has found differences between whites and negroes in the incidence of epilepsy, alcoholism, neurosis, psychosis, etc., but all the differences were explicable on other grounds than of racial inborn factors.

Manic-Depressive Psychoses.

Little new work is to hand on this subject, the most interesting being a report by Tomasson (1941). Tomasson had personally seen nearly all the manic-depressives in Iceland for the past nine years. Annual incidence is about 0·14 per cent., and the total probability of developing the disease before

70 is 0·07, i.e. about 20 times higher than in other countries for which statistics are available. All the descendants of the grandparents of 25 manic-depressives were investigated, comprising 2,463 individuals; in this group the frequencies both of manic-depressive psychoses and of psychiatric abnormality were no greater than in the general population. Among the sibs of the propositi 7 per cent. were manic-depressive, corresponding to the general Icelandic population, and to the frequency of manic-depressive psychoses in the sibs of manic-depressives as observed by Rüdin and Strömgren. The author considers his findings throw doubt on the significance of any heredity factor in the aetiology of manic-depressive psychoses. The results are anomalous, and the Icelandic population is a small and isolated one in which the distribution of genes may well be different from what it is in larger inter-breeding communities. Accordingly, any theoretical conclusions would be premature.

Myerson and Boyle (1941) have investigated the incidence of insanity in the families of certain socially important and wealthy individuals admitted to a superior private mental hospital in New England. They quote the observation of Landis and Page that "manic-depressive psychoses are responsible for 16·7 per cent. of first admissions to private hospitals and only 12·9 per cent. of first admissions to state hospitals. They add that manic-depressive psychoses are many times as frequent as schizophrenia in private consultative work. Their observations tend to support the idea that manic-depressive psychoses have a superior social distribution. In the first six families studied, they found 31 manic-depressives to 5 questionable schizophrenics. The families included state governors, members of Congress and Senate, ambassadors, etc., and other talented executives. The authors emphasize the value of a hypomanic temperament or hypomanic periods for great achievement.

Schmidt-Kehl (1939) has investigated the frequency of manic-depressive psychoses in the grandchildren of manic-depressives. The material, which is very small, yields an expectation of 24 per cent. for the children and 3 per cent. for the grandchildren.

Endogenous Psychoses.

German workers continue to accumulate the results of investigation of the frequency of the endogenous psychoses in the general population. Any one such individual investigation is necessarily based on a relatively small sample and leads to inconclusive results, but as this work is accumulated the information becomes precise and reliable. Schade (1941) has investigated the frequency of neurological and skeletal abnormalities in an isolated peasant population; the report is in summarized form. The work of Grobig (1939) has already been referred to.

Formanek (1939*a*) has given a provisional report on an investigation into the relatives of persons suffering from symptomatic psychoses. Fifteen thousand such cases were gathered from all over Germany, 500 specially chosen, and the data on the first 117 are given. The incidence of endogenous psychoses was very high—8·4 per cent. in the sibs—suggesting that a high proportion of the "symptomatic" psychoses were, in fact, endogenous. The paper meets with criticism from Bostroem and Thiele, which appears to be justified only

in part. Formanek (1939*b*) has also described the family of two parents, one of whom had schizophrenia and the other a pure delirium. One of the children developed a chronic paranoid schizophrenia, the other six remained well.

Kraulis (1939) has made an interesting collection of psychotic patients related to one another either as sibs or as parent and child. He gives a detailed clinical description of many of his 66 families, from which one may agree that manic-depressive, schizophrenic, and atypical psychoses may occur in the same family, and that clinical similarities may run across the classical delimitation of clinical types. Kraulis considers that schizophrenia and cyclothymia are probably genetically related, and the distinction between them is quantitative rather than qualitative. It is to be regretted that he has not given some details of all his patients instead of only a selection. Had he followed Zehnder's example, further use of his material for comparison and analysis would have been possible. Systematic collections of this kind are so expensive and time-consuming that they are worth reporting *in extenso*.

Hobbs (1941) has described five pairs of discordant twins of assured uniovularity. In two pairs injury to the brain at birth had produced in the one mental defect, in the other epilepsy. In one pair no environmental cause could be found for the development of *petit mal*. In another pair one sister developed hysterical symptoms, which are associated by the author with a more aggressive and intolerant temperament than that shown by her twin. In the most interesting pair of all a severe depressive illness seems to have been precipitated by psychogenic factors.

Pollock, Malzberg and Fuller (1939) and Pollock and Malzberg (1940) have described their investigations into hereditary and environmental factors in the causation of manic-depressive psychoses and dementia praecox. The first of these reports is a book of 460 pages. The psychiatric social work which has provided the data is slipshod; the genetic principles on which the analysis is carried out are out of date; the statistical treatment involves one fundamental error. The conclusions, which are drawn with great caution, amount to nothing.

Brockhausen (1939) has investigated the first and second degree relatives of 201 propositi suffering from involutional depressive psychoses. Where the illness was of a phasic and recurrent form, the incidence of manic-depressive and schizophrenic psychoses in the relatives was very much what it might have been expected to be had the propositi been ordinary manic-depressives. These excluded, the remainder of the material is divided into two groups of persons with and without a well-marked paranoid colouring to the psychosis. Both groups show a much lower incidence of manic-depressive psychoses than the phasic cases; the chief difference between them lay in the higher incidence of schizophrenic psychoses in the relatives of the paranoid patients. The author concludes that the non-phasic, non-recurrent depressive psychoses of the involution cannot be considered as manic-depressive in nature.

Leonhard (1939) has provided an interesting discussion of the atypical psychoses (Kleist's formulation). He considers that most of these forms are to be regarded as endogenous, and says that many show a higher degree of tainting than schizophrenic psychoses; he has observed that whenever he

finds the relatives of a schizophrenic to show a high incidence of psychosis the psychotic pictures are nearly always atypical.

Organic Psychoses.

The work done on the organic psychoses is small in volume and mostly of a non-systematic kind. English (1942) has described seven cases of Alzheimer's disease with clinical and pathological findings. In four of these the family history was negative, in one unobtainable; in the remaining two the mode of inheritance resembled simple dominance with irregular expression. McMenemey, Worster-Drought, Flind and Williams (1939) have described another case with clinical and pathological findings. The father and paternal uncle developed early dementia, a paternal aunt melancholia. Grünthal and Wenger (1939) have described a family in which the father and three children showed symptoms of Alzheimer's disease. Two of these were personally investigated, and in one the pathological findings are available. The suggestion of a fundamentally dominant mode of inheritance has therefore some support. Hadley (1941) has briefly described two Huntington families, without points of interest. Entres (1939) has carried out a systematic investigation of the 549 sibs of 108 propositi with Huntington's chorea. New points of theoretical interest are not raised. The characteristic simple dominant inheritance is confirmed and a manifestation rate approaching the 100 per cent. level is demonstrated. Pohlisch (1941) points out that Huntington's chorea shows a phenotypic variation with age. The normal age of onset is 35, and then choreic symptoms are the main disturbance; in the twenties a striate rigidity, in the sixties an intention tremor occupy a more prominent position in the picture. It would have been interesting if Entres had examined his large material from this point of view. Once again one must emphasize the desirability of a case-by-case presentation of a systematic collection. Sanders (1941) has briefly described a family of which 16 members suffered from Pick's disease. By responses to Rorschach and intelligence tests, she was able provisionally to recognize some members who only developed a typical picture eighteen months later. The mode of inheritance, as has been found elsewhere, was typically dominant. The family is probably the same as that reported by Sanders, Schenk and van Veen (1939).

Epilepsy.

Investigation of the genetics of epilepsy has been revolutionized by the advent of the electro-encephalograph, and Lennox, Gibbs and Gibbs deserve credit for their pioneer work in its application in this field. A preliminary account of their work was published in 1939 and a fuller description in 1940. They examined 183 relatives of 94 epileptic propositi, and found that 60 per cent. had an abnormal EEG. The findings in the case of the parents were: Both parents abnormal, 19; one abnormal, one doubtful, 5; one abnormal, one normal, 25; one doubtful, one normal, 3; both normal, 3. As they point out, the findings suggest that cerebral dysrhythmia is inherited as a simple dominant. Grounds for objection lie in the fact that the criteria of an abnormal

EEG are still unsettled among electro-encephalographers, and vary from observer to observer. Different criteria are, for instance, used by Lowenbach (1939), who found abnormal records in 17 out of 37 relatives of two epileptics, by Strauss, Rahm and Barrera (1939), who found in the families of 31 epileptics 7 out of 30 parents and 18 out of 63 sibs had abnormal EEGs, and by Robinson (1940), who in the relatives of 15 epileptics found 3 out of 20 parents and 9 out of 15 sibs had abnormal EEGs. Strauss *et al.* consider that epileptics can be divided into two groups, those with and those without abnormal EEGs in their relatives. Investigations of the twins of epileptics have been reported by Lennox, Gibbs and Gibbs (1942) in summary form. They show that the diagnosis of ovularity can be made with a high degree of certainty by the EEG. They report 15 pairs of epileptic twins, of whom 11 were uniovular. Seven of these were discordant as regards epilepsy, but concordant in the electrical abnormalities. In only one pair was one twin normal in every respect, while the twin sister had fits and showed a focal dysrhythmia; this patient recovered after six months. In this paper also the authors add further results to their investigations of parents of epileptics, which now reach: both parents abnormal, 43; one abnormal, the other doubtful or normal, 71; both normal or doubtful, 40. These are approximately the proportions one would expect if dysrhythmia were due to a single dominant gene with incomplete manifestation.

Lennox (1942) has examined the relationship between epilepsy and mental defect. He found that of 1,905 epileptic patients 2 per cent. were of above average intelligence, 62 per cent. average, 22 per cent. slightly sub-average, 12 per cent. definitely, and 2 per cent. markedly deteriorated. This is obviously a very abnormal distribution. If epileptic seizures and mental defect have any common genetic basis, defective epileptics should have a larger frequency of affected relatives than mentally normal epileptics, and the evidence should be strongest in those in whom mental defect was present from birth. He finds the incidence of epilepsy among the relatives of epileptics to be: of those mentally defective at birth, 5·9 per cent.; of those normal at birth and now deteriorated, 3 per cent.; of those normal at birth and now, 2·4 per cent. The effectiveness of the hereditary factor is likely to be shown in early onset of seizures. The frequency of epilepsy among the mentally defective epileptics whose fits began between 0 and 4 is 8·8 per cent.; 5 to 9, 7·0 per cent.; 10 to 19, 5·1 per cent. Among the relatives of those normal at birth the corresponding frequencies are: 0 to 4, 4·3 per cent.; 5 to 9, 2·7 per cent.; 10 to 19, 2·6 per cent.; 20 to 29, 1·7 per cent.; 30 and over, 1·0 per cent. This evidence, though expressed in a statistically objectionable form, seems to be important. The genetic interpretation, however, is possible along many lines.

The views of Lennox, Gibbs and Gibbs on the inheritance of epilepsy may be summarized as follows. Both symptomatic and idiopathic epilepsy will as a rule not occur without the physiological basis of a dysrhythmic brain. The tendency to dysrhythmia of the appropriate kind is inherited as a simple dominant. Epilepsy may then be released by the impact of the environment in some form. A development of this theory, which has much to recommend it

for its simplicity, has been suggested by Whitteridge (1942), i.e. that the manifestation of epilepsy will depend as a rule on the dysrhythmic gene being present homozygotically. We have not yet sufficient data for judgment to be passed on these hypotheses.

Neurosis and Psychopathy.

It seems likely that electro-encephalographic work will also throw light on the genetics of psychopathic personality, as is instanced by the work of Hill and Watterson (1942), who found that of 151 psychopaths of all kinds 48 per cent. had abnormal EEGs, and that of a more restricted group of 66 aggressive psychopaths 65 per cent. had abnormal EEGs.

Felix Brown (1942) has reported an inquiry into the family history of a group of patients suffering from anxiety state, hysteria, and obsessional neurosis, and also of a group of controls. In the parents of the patients, the frequencies of anxiety states, hysteria and obsessional neurosis were respectively: I (anxiety neurotics), 21·4 per cent., 1·6 per cent., 0·0 per cent.; II (hysterics), 9·5 per cent., 19·0 per cent., 0·0 per cent.; III (obsessional neurotics), 0·0 per cent., 0·0 per cent., 7·5 per cent. The corresponding figures in the sibs are, in the same order: I, 12·3 per cent., 2·2 per cent., 0·9 per cent.; II, 4·6 per cent., 6·2 per cent., 0·0 per cent.; III, 5·4 per cent., 0·0 per cent., 7·1 per cent. There were also considerable incidence rates of depressive states and of persons of abnormal personality in the relatives of all groups. Brown concludes that, while his findings are against any simple Mendelian inheritance, they are practically conclusive of the significance of hereditary factors. The importance of the environment cannot, however, be neglected. The three types of neurotic state distinguished are probably genetically related to one another, and the development of a neurosis probably depends on the combination of a number of distinct genes, many or all of which in other combinations may be compatible with normal psychiatric make-ups.

The problems of genetic investigation have been discussed in general terms by Stumpfl (1939*a*, *b*). No factual data are provided. The same is true of Riedel's long paper (1939). He says that in studying two groups of psychopaths, "geltungsüchtige" and "asthenische," roughly comparable to the hysterical and inadequate types of British psychiatry, he has found very different familial relationships. The specific qualities that characterized the first were five times as common among their relatives as was the case with the second group. Schröder (1939) has described six pairs of female twins, of whom at least one had drifted into a life of profligacy during or soon after adolescence. Two of these pairs were binovular and concordant, both in respect of character and social behaviour. The remainder were binovular, and of them three showed a considerable degree of discordance in both respects, while one was concordant. The author considers that the sexual downfall of young girls depends to a considerable extent on their personalities.

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* Of no significance for this study.
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