THE INHERITANCE OF MANIC-DEPRESSIVE INSANITY AND ITS RELATION TO MENTAL DEFECT.

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IN the development of psychiatric genetics progress has been very largely dependent on the progress of clinical psychiatry. In the early days the theory of polymorphism held the field—that is the idea that there is a single hereditary basis for what may be called degeneration, which might show itself in many forms, any form of insanity, psychopathic character, criminality or mental defect. This theory was built up on the unclear psychiatry of the day, when the boundaries between different clinical states were vaguely drawn and largely in dispute. We are now passing out of this stage in clinical psychiatry, but the genetic theory that was built on it, the idea of polymorphism, still lingers on. It has been the stimulus to an immense amount of muddled research of no value. The time has come when this theory should be finally discarded. We are not entitled to think that different clinical conditions have the same genetic basis until such has been proved. From a factual point of view the accumulation of knowledge has shown it in a number of cases to be untenable. From a heuristic point of view it offers no possibilities of advance.

The task of psychiatric genetics is immense. It consists in the examination of the single clinical syndromes, to show whether they are genetic unities or not, the proof of a hereditary basis for every such syndrome where it exists, the investigation of its method of inheritance, whether dominant or recessive, autosomal or sex-linked, whether dependent on one or more genes, whether it is linked with any other known factors, its capacity for manifestation, its specificity, the measuring of the influence of the environment and the analysis of this influence, and finally as a direct aid to clinical psychiatry, the clearing up of the clinical picture into the essential features which are directly dependent on the hereditary factor in question, and the inessential features as they are introduced into the picture either as the manifestation of other accidentally present hereditary factors or as a result of the influence of the environment. I think we shall find that in the majority of psychiatric states the essential and specific quality is dependent on one or more hereditary factors. It may well be, for instance, that the reason one syphilitic develops general paralysis and another does not will be found to rest on a hereditary factor following within limits Mendelian laws.

Turning to the inheritance of the manic-depressive psychosis, the investigator is faced with peculiar difficulties. The exact delimitation of this psychosis,

or perhaps group of psychoses, is still unclear. On the one side many would include in it the psychogenic depressions of the unstable psychopathic character, or on the other side almost any endogenous psychosis showing strong affective features, however complicated by paranoid ideas, hallucinatory experiences, or symptoms characteristic of a schizophrenic or more definitely organic illness. In the investigation of such a syndrome it is essential to leave disputed ground out of account. It may be that these outlying conditions have near or remote genetic connections with what one might call the central group of manic-depressives. It is one of the services of psychiatric genetics to have shown that what is commonly called involutional melancholia has nearer connections with the schizophrenic psychoses than with the manic-depressives. In an investigation of manic-depressive insanity only the indisputable cases should be included as part of the working material. These other outlying conditions should be investigated singly and for themselves to show whether they have any connection with manic-depressive insanity or not.

In a paper recently read before the Royal Society of Medicine I described an investigation into such a central group of manic-depressives. It may be worth while here briefly to summarize my results. The total material amounted to 879 parents and children who had passed the age of twenty years; I found:

109 cases of manic-depressive insanity and of suicide where a manic-depressive psychosis might be suspected.

68 cycloid psychopaths, that is, people showing such endogenous swings of mood as to be reminiscent of the psychosis, without themselves ever having been ill enough to have required treatment.

11 schizophrenics.

8 epileptics.

5 imbeciles.

The results seem to me more than suggestive of the specificity of the manic-depressive hereditary factor. While the incidence of manic-depressive insanity was high, as was also that of that type of character which one must assume to be related to it, the incidence of other conditions was, with the exception of schizophrenia, hardly higher than one would find in the general population. As regards the incidence of schizophrenia, I found that while the incidence among the parents was very small indeed, it was appreciably greater than might be expected among the children. It may be that the small incidence among the parents is merely due to the reduced fertility of schizophrenics. Dividing my material up into the cases with the purest manic-depressive symptomatology, and those with a slight colouring of foreign symptoms, I found much the higher incidence of schizophrenia among the children in the latter group. In other words the more strictly one defines the group, the more pure is the psychosis found to run in the families. The incidence of manic-depressive insanity among the parents and the children was respectively about 16 and 13%. The frequency of direct inheritance is such as to suggest

a dominant inheritance, which is not, one might think, supported by the wide divergence of my findings from the expected Mendelian proportions. I think that this would be a short-sighted way of looking at the results. There are so many sources of error, difficulties of ascertainment, incompleteness of information, statistical difficulties, that one would expect the actual findings to be considerably less than expectation. In addition, the results of what twin-studies have been made hitherto are such as to suggest that not much more than 70% of the genotypic manic-depressives ever show themselves as phenotypically so. In addition I have given reasons elsewhere for thinking that genetic modifying factors may well play a part. For instance the following facts are, I think, highly suggestive of such a theory. According to the previous work of German authors, the incidence of manic-depressive insanity among the relatives of manic-depressives is as follows:

Among the parents and siblings 10–12%.
,, uncles and aunts about 5%.
,, cousins about 2½%.

These figures being more or less in the ratio 4 : 2 : 1 are just what one would expect with a single factor inheritance. The suggestion is that whatever factors are responsible for the reduction of the incidence of manic-depressive insanity among the relatives below theoretical expectation, they are equally operative in the nearer and more distant relatives. Environmental influences and the influence of unrelated genetic modifying factors are just the ones that would have this causal effect, equally operative in every case. In each case, parents and sibs, uncles and aunts and cousins, the finding is just about one-fifth of that required by a theory of a single dominant autosomal factor. If one assumes that the 50% incidence demanded by theory among parents and sibs is reduced by environmental influences, as suggested by twin studies, to 35%, that insufficient ascertainment accounts for a certain further reduction of the findings, and finally that independently inherited genetic modifying factors are responsible for the rest, the gulf to be bridged is not such a wide one, and the findings are readily explicable. On the other hand, any theory relying on two or more factors is powerless to explain this ratio I have mentioned of 4 : 2 : 1.

It is a well-known principle that one should adopt the simplest theories until more complex ones have shown themselves to be necessary. Nearly all the hereditary diseases of man which have been well investigated hitherto have proved explicable by theories involving a single factor dominant or recessive, autosomal or sex-linked. I believe that this will continue to be the case with psychiatric disorders, not only manic-depressive insanity, but schizophrenia and epilepsy, and that our present difficulties arise from the practical difficulties of investigation, from lack of genetic uniformity in the material selected for research, and in the influence of modifying factors. That such modifying factors do play a part in the inheritance of the majority of heritable anomalies

has been amply proved in the far more accurate and reliable results of animal genetics, particularly by the work on *Drosophila*. In my opinion this simple, single-factor inheritance may well show itself in every case where an individual either shows a certain condition or not. A man is either hæmophiliac or not, either epileptic or not, and in my opinion either manic-depressive or not. That we may not always be able to give a certain answer in an individual case is a different matter. Of course when one comes to the inheritance of stature or other qualities where it is a matter of degree and not of a simple positive or negative, other and more complex theories will no doubt be required.

It will be seen that I support in the first place the specificity of the hereditary factors for psychiatric illness as exemplified by manic-depressive insanity. This attitude has recently been attacked in a paper published by Drs. Duncan, Penrose and Turnbull. The authors remark: "The supposition is often made that the same kind of mental trouble is found in different members of the same family. Little evidence for this view has, however, been obtained from the examination of pairs of brothers and sisters who are in the hospital. From the clinical point of view mental disease is not very true to type. For example the known relatives of our manic-depressive patients were more frequently schizophrenic than manic-depressive." This is a return to the old polymorphism. I should like to suggest that their findings are due to an insufficiently strict definition of their clinical groups. I should like to ask the authors how many cases of involutional melancholia there were among their manic-depressives, and how many other cases showed symptomatic anomalies. I do not accept, as apparently they do, the presence of auditory and even visual hallucinations in a patient unfuddled by fever, drugs or the beginning of an organic illness, as at all frequent symptoms for a manic-depressive to show. For their statement that mental disease is not true to type the authors bring no other evidence than the statements quoted above. I should like to ask them, Did they find as many epileptics among the families of manic-depressives as among the families of epileptics? And did they find as many manic-depressives among the families of the schizophrenics as among the families of the manic-depressives?

Part of the subject of my paper to-day is the relation of manic-depressive insanity to mental defect. The main part of the paper of Drs. Duncan, Penrose and Turnbull, already referred to, deals with this very point. The authors examined the 2,134 patients who made up the standing population of a large mental hospital, and also the 463 patients who were admitted to it during the year 1934. They found in the standing population the following percentages of mentally defective patients, correct to the nearest per cent.:

Of the schizophrenics	38%	dull or defective.
manic-depressives	46%	,, ,,
epileptics	66%	,, ,,
organic psychoses	22%	,, ,,

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and among the new admissions:

Of the schizophrenics	24%	dull or defective.
manic-depressives	27%	,, ,,
epileptics	60%	,, ,,
organic psychoses	22%	,, ,,

The authors give separate figures for the different grades of defect. For instance, of the manic-depressives who were permanent inmates, 24·4% were mentally defective, and 6% of the fresh admissions. By mentally defective the authors state they mean certifiably so.

These findings must have come as a surprise to everyone who read them. The percentages are extremely high, and if they are accepted as representing a general truth, then it would seem that there is a general connection between mental defect and all forms of mental disorder. Unfortunately this part of the authors' work does not seem to me above all possible criticism. It is obvious that working in a rate-aided mental hospital in the country one will be dealing at the start with a population selected by purely adventitious circumstances, probably favourable for mental defect. The percentage of mental defect, however, found by the authors is so high that it could not correspond to any community living outside an institution. This criticism, then, hardly meets the point. Even if they could expect to find more defectiveness than in the general population, they could not have been expected to find all that amount.

Their methods of diagnosis of dullness and mental defect are, however, open to more serious objection. They report they used "a few standardized questions out of Burt", and backed this up by taking note of the school record. It will be remembered that a competent psychologist doing an individual test will take about ½–1 hour to assess the intelligence of a normal individual, using a whole battery of tests, all of which have been standardized. I should like to ask, Have the standardized questions used by the authors ever been used by themselves before? If they have been taken out of a complex of tests their standardization no longer exists, and they are no reliable test of intelligence, even for a normal individual. In any case "a few standardized questions" do not compare in strictness of testing with the prolonged series of tasks and questions given by the psychologists in testing a normal individual. But the material in this case was not that of normal and co-operative school-children, but the population of an asylum, and presumably consisted to a large extent of stuporose catatonics, self-absorbed and hallucinating hebephrenics, suspicious paranoiacs, scatter-brained and distractible manics, and worried and retarded depressives. It is surprising that anyone at all under such circumstances reached a standard of normality. I would suggest that psychological tests of intelligence on such people are useless. If one takes no account of psychiatric causes of failure to come up to normal, one is grossly misrepresenting the material and not testing intelligence at all. If one does take such

account, one's judgment becomes in effect quite subjective, and the subjective valuation of the patient's intelligence is likely to vary with the time taken and patience of the examiner.

One would wish to know under these circumstances on what proportion of cases the diagnosis of dullness or defectiveness was based on these tests alone, and in what proportion there was a backing of a history of failure at school. It is to be hoped that in the organic cases the authors did not use the tests at all, as it is impossible to tell in a given case where defect ends and dementia begins. In these cases one must assume that the diagnosis was based solely on the school record. But is this again a reliable test of mental defect? I think not. In an investigation I shall have occasion to refer to again, Juda followed up about 500 children who had repeated two classes at school. This about corresponds to Drs. Duncan, Penrose and Turnbull's standard of not having reached the fifth standard by the age of fourteen as sufficient evidence of certifiable mental defect. In about half of these children she found that other causes, such as physical illness, could not be excluded as the cause of this educational failure, and that of the remaining 50%, where there was no apparent cause of failure, 3% of the persons were all the same of normal intelligence, some 28% were "schwach begabt" or "debil", which about correspond to the standard of dull and backward of English authors, and that only the remaining 19% were of such a degree of defect as to be "imbezill", which is the German equivalent of feeble-mindedness or higher degree of certifiable mental defect. This would suggest that, using comparable standards to those of Drs. Duncan, Penrose and Turnbull, only about 20% of those whom, owing to failure at school, they would classify as certifiably mentally defective may actually have been so.

It might be profitable here to turn to the English legal definition of certifiable mental defect. Feeble-minded persons are those "in whose case there exists mental defectiveness, which though not amounting to imbecility, is yet so pronounced that they are incapable of managing themselves or their affairs, or in the case of children, of being taught to do so". It seems to me that any person who has been capable of following any employment up to the time in which he became psychotic, of earning his living and supporting himself in the outside world, or in the case of women, of managing a household, should not be regarded as certifiably mentally defective. How many of the cases which were diagnosed by Drs. Duncan, Penrose and Turnbull as mentally defective, that is as feeble-minded or worse, gave histories of having been unable to manage themselves or their affairs?

There is one other point in this paper to which I should like to refer. The authors provide a table giving the incidence of mental deficiency or disease among the near relatives of the resident patients. The figures are expressed as the number of affected parents or sibs per patient. Thus there were 94 affected sibs of the 287 manic-depressive patients, giving an "incidence" of

0·327 affected sibs per patient. These figures are compared with the figures obtained by Luxemburger and Schulz for the expectation of mental disease for any individual in the general population. The comparison is impossible, and the figures given by the authors are meaningless. The number of affected sibs per patient is obviously largely dependent on the total number of sibs. If manic-depressives tend to come from larger families than schizophrenics, they will for that reason alone tend to have a larger number of affected sibs per patient. What is required is the incidence of mental abnormality among the sibs of the various diagnostic groups, a figure that will be a function not only of the number of affected sibs found, but also of the total number of sibs and their age distribution.

Unfortunately the paper of Drs. Duncan, Penrose and Turnbull is the only one I know of that directly attacks the problem of a possible relationship between manic-depressive insanity and mental defect, and the answer they give is not to my mind satisfying. What other investigations there are bear less directly on the point, and the answer given is one contrary to theirs. Luxemburger explained the relationship between psychosis and social class. His figures were obtained from a psychiatric clinic in Germany, to which patients are admitted entirely irrespective of social position. He found manic-depressive insanity nearly three times as frequent in the highest social class, four times as frequent in the professional classes, as in the general population, while schizophrenia was over $1\frac{1}{2}$ times as frequent in the highest, and over twice as frequent in the professional classes as in the general population. In the lowest social class the frequency of both disorders was less than in the population as a whole. As against this, the highest social class showed $\frac{2}{5}$ and the professional classes $\frac{1}{5}$ of the incidence of mental defect in the general population, while the incidence of mental defect in the lowest class was higher than that in the population as a whole. Now the highest social classes are not free from mental defect, and it might be possible that insanity singles out the defectives of every class for attack; but even if this were true, it remains difficult to see why classes with a low frequency of defect show a high frequency of certain forms of insanity, while these forms of insanity are rarest in the class with the highest incidence of defect—that is to say, if the relationship suggested by the work of Drs. Duncan, Penrose and Turnbull did actually exist.

If it is correct that a high proportion of the insane are defective, one would expect to find that a relatively high proportion of the defective are insane. The evidence is against this. I must refer once more to the work of Juda. She followed up the 97 ex-school-children who had been failures at school without other obvious cause than possible mental defect, and found that all but 6 were dull and backward or feeble-minded. She also obtained all accessible data about their parents and their children. She thus collected 524 members of the families of a largely defective class, and was able to compare them with a group of 433 members of families of normal ex-school-children,

taken from the same schools at the same period of time. She found in the defectives' families 2 manic-depressives; one of them was one of those 6 ex-school-children who had been failures at school, and yet were not defective. In fact, then, she found in the families of the defectives only 1 manic-depressive; in the families of the normals there were 6. In the families of the defectives there was 1 cycloid psychopath; in the normal families 11. In the defective families there were 6 schizophrenics, in the normals 5; in the defective families 6 epileptics, in the normal families 1. Summarizing these results, then, epilepsy was nearly six times as common in defective families as in normals, schizophrenia was about the same in both, and manic-depressive insanity was over six times as frequent among the normal families as among the defectives.

The rather small evidence, then, that we have is such as to suggest a negative answer to the question, "Is there any relation between manic-depressive insanity and mental defect?" The suggestion rather is the reverse—that there is a positive association between manic-depressive hereditary traits and successful adaptation to life and society. Such a suggestion need not be very surprising. One can well understand that the warm affective relation to the human environment and the infectious spontaneous sympathy, with which the psychiatrist is familiar in dealing with true manic-depressives and their nearer relatives, should lead to a good adaptation to the environment as a whole, and if these are combined with the abundant flow of energy, which in its extreme form is seen in the hypomanic, how the possession of such qualities may even lead to success above the average.

References.—Duncan, A. G., Penrose, L. S., Turnbull, R. C., *Journ. Neur. and Psychopath.*, 1936, xvi, p. 225.—Juda, A., *Z. Neur.*, 1934, cli, p. 244.—Luxemburger, H., *Eugenik*, 1933, p. 3, —Slater, E., *Proc. Roy. Soc. Med.*, 1936, xxix, p. 981.

Discussion.

Dr. T. A. MUNRO said that after he had read the abstracts of Dr. Slater's and of Dr. Duncan's papers, he thought he could be of some use to this discussion by showing simply one pedigree of a family suffering from mental disorder. Having listened to Dr. Slater's paper he was encouraged to think he was right in choosing this form of contribution.

The chart he was exhibiting was that of a Suffolk family.

Several points were to be noted about that pedigree. Six generations were represented, and it would be seen that there was mental abnormality in the first five generations—the sixth was only now arriving. This mental disease affected some families, leaving others free. It would be seen that a person who was healthy had healthy children and healthy grandchildren, whereas a person who was insane had both children and grandchildren suffering from insanity. There was a further degree of order in this selection. In the second generation three out of seven brothers and sisters were insane. One of those insane persons had ten children, and of the eight of those who reached adult age in this third generation, four were psychotic. Those four psychotic people, in the next generation, had sixteen children, of whom seven showed mental abnormality. Similarly, in the

succeeding generation, of the nine offspring of these seven affected people, four were mentally abnormal.

Such an arrangement was consistent with the theory that a single dominant Mendelian factor was the main cause.

Another point worth noting was that the incidence of 50% affected did not vary on coming down the five generations, but remained constant, in spite of new blood coming in by marriage. In other words, there was no tendency for the disease to " breed out ".

Perhaps the most important point about this pedigree was that there was a remarkable similarity in the types of psychosis in those who were affected. All the abnormal people on the pedigree were mentally defective. With the exception of seven young mental defectives, all the abnormal members had had, in addition, one or more attacks of mania or depression, or both. He had not time to prove that to the meeting by case-records. One woman was unable to read or write, though her healthy brothers and sisters could do so. She could not look after her home. At the age of 32 she became excited and elated, believing that she was entitled to a legacy of £100. Later in the year she was depressed and suicidal. She was discharged from hospital recovered several times before she passed into a condition of chronic mania ten years before her death. Similarly her elder daughter, who was markedly feeble-minded, had a manic attack in which she thought she was an empress, and some years later she was melancholic, and went about asking people to forgive her her sins. Thus it would be seen that there was a definite psychosis of manic-depressive type, associated with mental defect. It might be important to notice that, with the exception of the feeble-minded people indicated, who were all young—the eldest was not yet 26 years of age—mental defect did not occur in the family by itself.

It would be possible to produce several families showing an association between manic-depressive insanity and mental defect, but it would be more easily possible to produce many families of manic-depressive disease in which there was no question of mental defect, members of which had, on the contrary, risen both socially and financially, and had made a big success of life in a worldly way. And it would be interesting to know if such socially-successful people were found in one or other type of family more commonly.

He thought many would agree that in collecting the family histories of mentally disordered persons, it was exceptional to get a history showing the order and the specificity of the psychosis which this chart showed. More often the distribution of mental abnormality seemed to be irregular, and the clinical type of psychosis varied widely. Schizophrenia, manic-depressive disease, senile dementia might jostle one another in seeming confusion, and, in general, it did not seem to him that order could be read into that, and it had not yet been shown that a high degree of specificity existed for the inheritance of mental disease, although, of course, such seeming confusion did not disprove it. From the practical point of view, he supposed it was of importance that in a family such as the one now demonstrated, one should look up the ancestors of all the people who came in by marriage. Such a task would greatly increase the work of taking family histories.

He wished to come to one practical point. He had been impressed, in doing work during the last 18 months in rural counties, by the comparative ease with which it was possible to obtain family histories of mentally disordered persons, owing to the fact that in most cases the families had lived and died in the same locality for generations past, and for scores of years the insane members of a family had gone to the same county mental hospital, where their records were available. This state of affairs—happy from the research point of view—was now rather rapidly changing, owing to the vast increase in road travel. He thought that in future years the practical difficulties of getting family histories would become rapidly greater, but at the present moment there existed a great opportunity for acquiring family histories in the areas supplied by the county mental hospitals.