Section of Psychiatry

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[*February* 11, 1936]

The Inheritance of Manic-depressive Insanity [1]

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ATTEMPTS are frequently made to base theories of the method of inheritance of psychiatric abnormalities on the statistics obtained from family investigations. For these theories to be worth consideration, it is necessary that the preliminary investigations should fulfil certain elementary requirements:—

(1) In the gathering of the material there should be no process of selection that is not scientifically justified, and clearly understood and stated by the author. (2) The original material should be, as regards the character investigated, genetically uniform. (3) The numbers of relatives investigated should be sufficiently large to reduce the errors of random sampling within reasonable limits. (4) All persons covered by the terms of reference should be included, and exhaustive, up-to-date and reliable information should be obtained about each and all of them. (5) The diagnosis of presence or absence of the character examined for should be sufficiently well founded to command general agreement among those qualified to judge. (6) The statistical working out should be free from objection.

Judged by these criteria there is no family investigation in psychiatry known to me that passes the test. Certain grave difficulties lie in the nature of the material itself. It is impossible to assure oneself of the genetic similarity of the material, but it is quite possible to attempt as close as possible a phenotypic similarity. Most authors do not take this nearly far enough. I may mention the many family investigations that have been made in schizophrenia, where practically no attempt has been made to attempt similarity of material. It is in the nature of work on human material, particularly in psychiatry, that exhaustive information about any one individual is really only to be obtained when he has been observed by experts over many years in a hospital. Anything less than this is only an approximation to what would be scientifically desirable. Nevertheless many authors are contented with much less information than would be available with more intensive work, and are ready to publish figures on such a basis, with the implicit assumption that their material is complete. When one considers that in only a minority of cases is the investigator lucky enough to obtain what knowledge he can in a short interview, and that in the often great majority he is compelled to rely on secondhand information, one is in a position to appreciate how shaky are the

[1] The work that is the subject of this paper was done during the tenure of a Rockefeller Fellowship.

"facts" on which the grandiose superstructure of psychiatric genetic theory has been built. These are what one might call the genetic difficulties. To them must be added the difficulties that arise from our lack of knowledge of what is fact and what is theory in psychiatry. Genetic investigations of twenty years ago would have included numbers of cases of "delusional insanity." This term has little meaning for us now. We have little right to assume that "schizophrenia," for instance, will have much more for our psychiatric descendants. Above all, we have little ground for supposing that the clinical entity, which is a matter of conception and convenience, and the supposed underlying genetic entity correspond. To all these difficulties, genetic and psychiatric, must be added the practical difficulties of the investigation itself, the necessity for the investigator to reach a diagnosis on inadequate material, the impossibility of excluding the influence of preconceptions on judgment, the highly inadequate and often frequently slipshod statistical methods so often employed. The criteria I have outlined above would be difficult to satisfy in their entirety, but much of the unsatisfactory character of family investigations in psychiatry hitherto is due to the investigators either having little idea that these requirements should be filled, or in any case making but a poor approach to their fulfilment.

The present knowledge of the inheritance of manic-depressive insanity is based on the work of Rüdin (1923), Hoffmann (1921), Banse (1929), and on the work of Luxenburger (1932) summarizing and editing the data of others, including those of Entres and Roll (unpublished). The investigations of Rüdin have never been published, and cannot be criticized. The work of Hoffmann is especially important, because of the very heavy incidence of manic-depressive psychosis he gives for the children of manic-depressives. Judged, however, by the criteria I have suggested above, his work fails to satisfy one of them. There is no sign that Hoffmann made any attempt to secure uniformity of material; his numbers are small and unsatisfactory for statistical working out; not more than one member of the family was seen in any case; the amount of information obtained, at least that which he prints, is very inadequate; above all, his diagnosis of manic-depressive insanity among the children he investigated is such as to command general disagreement. Apparently led by a Kretschmerian psychiatry, he includes among manic-depressives all persons in any way subject to swings of mood, however socially well adapted and unremarkable they may be, and he includes among slighter degrees of hypomanic and depressive temperaments such persons as he describes as "quiet humorists." It is possible that such people as quiet humorists are found more frequently among the relatives of manic-depressives than in the general population; this remains to be proved; but it gives no right to rank them with persons showing well-marked cyclic character traits as carriers of manic-depressive hereditary elements. The very heavy incidence of manic-depressive insanity among the children of manic-depressives found by Hoffmann seems to me to be largely explained by his tendency to exaggerate normals into abnormals, and mild character deviations into psychoses. The most cogent criticisms on psychiatric grounds have already been made on Hoffmann's work by Wilmanns (1922) and Meyer-Gross (1925), and I will not go into the matter further. Finally, Hoffmann did not attempt any adequate statistical evaluation of his material, and though Luxenburger has subsequently attempted to treat his figures so as to make them comparable with the figures obtained by others, I do not think that Hoffmann's material can stand the strain.

Banse's work on the cousins of manic-depressives is free from the psychiatric objections to which Hoffmann's work is open, but is of dubious statistical value. Banse admits that among the 1,586 cousins he includes in his material he obtained personal information about less than two-fifths: data about the rest were obtained from the use of records, family trees collected in previous years, odd facts jotted down in the case records, &c. This limits the value of his work very much.

Luxenburger collates his work with that of Hoffmann, Rüdin, and other workers in the following table :—

TABLE I.—INCIDENCE OF MANIC-DEPRESSIVE INSANITY AMONG RELATIVES OF MANIC-DEPRESSIVES. (AFTER LUXENBURGER)

Relationship	Number of persons investigated	Percentage of manic-depressive psychosis
Children	165	30·2
Nephews and nieces ...	452	2·6
Cousins	867	2·7
Brothers and sisters ...	263	12·6
Parents	170	10·6
Uncles and aunts	559	4·8

The investigation that forms the basis of this paper was carried out at the " Deutsche Forschüngsanstalt für Psychiatrie " in Münich, with the kind permission of Professor Rüdin, who placed the resources of his institute at my disposal. I should first like to pay a tribute to the magnificent organization of this research institute, without which it would have been unthinkable for a foreigner to attempt such an investigation in a strange land. Summaries of all the cases admitted to Kraepelin's clinic in Münich between the years of 1904 and 1922 are kept on file at the psychiatric research institute. Of these records some 3,000 referred to cases diagnosed as manic-depressive. I read through these records and selected cases which fulfilled certain conditions. It was my hope at that time to investigate that group of manic depressives who show in the appearance and remission of illness a certain ordered rhythm. There seemed to be a possibility that these persons might show peculiar relations in the matter of heredity. Unfortunately, though there were such cases, they were extremely few in number, and insufficient for statistical work. Accordingly I was reduced to selecting any cases which showed some degree of phasic recurrence, the conditions at last decided on being that they had had at least either one clear manic and one depressive attack, or three separate depressive or manic illnesses. I neglected all cases in which the first illness had appeared in the fiftieth year or subsequently, so as to eliminate the dubious involutional and arteriosclerotic cases. About half-way through the investigation, a few more cases filling my conditions were obtained from Eglfing, the Münich mental hospital. Of such cases I collected, in the end, 315, of whom 114 proved to be childless. The relatives of the remainder were then written to, and I saw as many of the children of the original case in every family as I could. Of the 201 families with children I was able in 41 cases to get no direct information from any member of the family. Although in one or two of these cases this was due to every member of the family having died, and in others very complete information was available on file at the institute, I have thought it better to exclude them all from my statistics about the children. In the remaining 161 families I obtained information from 157 personal interviews and 62 written communications (in 172 cases from children and in 47 from other members of the family). In most instances these interviews and letters served to complete the very extensive information already in possession of the institute. For information about parents I have not restricted myself to these personally investigated cases, as the documentary evidence was already complete, and could in any case be but little supplemented by information from grandchildren.

I have, however, subjected my material to other processes of selection. In the original selection of the cases I was satisfied in taking the Kraepelinian diagnosis as it stood, without paying close attention to the symptomatology. It is, however, well known that at one time Kraepelin purposely expanded his diagnosis of manic-depressive insanity to include as many cases as possible, subsequently testing the validity of the diagnosis by follow-up records. When, after a few months, I attempted a provisional estimation of the material, I was surprised to find a number of schizo-

phrenics among the children. It seemed possible that this might be in part due to incorrect diagnosis in the original cases. It is, for instance, only in recent years that the attention of clinicians has been drawn to remitting forms of schizophrenia, and the course of an illness is now no longer considered sufficient as the only criterion for the diagnosis of manic-depressive psychosis. Accordingly I completed the collection of my material, and have subsequently attempted to subclassify it according to the clinical picture presented by the propositus, so as to isolate out cases where error might be introduced through incorrect diagnosis. In this process I have availed myself extensively of the help of colleagues, particularly of Drs. Mayer-Gross and Guttmann, and have in no case ventured myself to decide on the final diagnosis of a case, where I knew of the presence of a schizophrenic child, but, to avoid any possible partiality, have in every such case relied on the judgment of others.

The incidence of any abnormality appearing late in life is to a great extent dependent on the age-distribution of the population in which it occurs. It is essential to employ some statistical device to remove this disturbing factor. The method in use in Germany is, in the case of manic-depressive insanity, to neglect all members of the population in question who have not reached the age of 20, as having had no chance of developing the illness, to count as half all those between the ages of 20 and 50, and to count in full all those above 50. For this to be fully justified, no persons should develop the illness before 20 or after 50, while the chance in the intermediate years should be about the same for any year, and the population in question should show a similar even distribution between these years. Although the fundamental assumptions for this device are difficult to justify, it seems likely that the employment of this method does not give rise to any gross source of error, at any rate not comparable to the many other grosser sources of error which I have pointed out above. As my cases, however, showed in some groups a somewhat uneven distribution between the ages of 20 and 50, I have preferred to divide them up into five-year groups, and take the number in each group as being concentrated at its mean. Thus a group of people between the ages of 20 and 25 would be reckoned as of age $22\frac{1}{2}$, and considered to have lived two and a half of the thirty years in which they might show themselves as manic-depressive, i.e. their number would be divided by 12. Similarly the number of those in the 45 to 50 group would be multiplied by the fraction $\frac{1}{12}$.

The exact clinical interpretation of the cases with children necessitated obtaining the full record from the psychiatric clinic, and the clinical records from many other mental hospitals, and an up-to-date catamnesis on every case. As a result of this I was eventually placed in possession of an immense amount of clinical material which I hope to be able to use for other purposes. As a result of this more exact examination of the material, I have eliminated from the 201 families 20 in which the diagnosis of manic-depressive insanity seemed to be altogether incorrect, and I have further separated a special group of 41 cases in which both manic-depressive and schizophrenic symptomatology was shown clearly in the record. It is hoped to subject these last to special study. The remaining 140 cases I divided into two groups: firstly a group of 72 cases (Group I), in which the symptomatology was not only clearly manic-depressive, but purely so, and unaffected by organic or schizophrenic-like disturbing elements; and secondly a group of 68 cases (Group II), in which such disturbing elements did enter, but not in any sufficient amount to throw the diagnosis of manic-depressive insanity in any doubt. Among such foreign symptoms I included greater irritability than usual, a somewhat paranoid attitude to the environment, exaggerated hypochondriasis, any episode of apparently exogenous origin, such as a period of confusion accompanied perhaps by delirious hallucinations. Cases where there were hallucinations in a state of clear consciousness are not included.

My material falls, then, into three groups of parents—those of the childless manic-depressives who were subject to no special investigation, and the parents of Groups I and II; the children are classified in Groups I and II only. I give the results in Tables II and III.

TABLE II.—INCIDENCE OF PSYCHIATRIC ABNORMALITY AMONG PARENTS OF MANIC-DEPRESSIVES.*

	Childless group (225)		Group I (141)		Group II (129)		All groups (495)	
	%	S.D.	%	S.D.	%	S.D.	%	S.D.
Manic-depressives ...	15·6	2·4	13·5	3·0	17·1	3·3	15·4	1·6
Cycloid psychopaths ...	3·1	1·1	2·5	1·3	5·1	1·7	3·8	0·7
Schizophrenics	1·3	0·8	0·7	0·7	0·0	0·0	0·8	0·4

TABLE III.—INCIDENCE OF PSYCHIATRIC ABNORMALITY AMONG CHILDREN OF MANIC-DEPRESSIVES

	Group I (116)		Group II (93)		Both groups (209)	
	%	S.D.	%	S.D.	%	S.D.
Manic-depressives ...	15·5	3·4	16·1	3·8	15·8	2·5
Cycloid psychopaths ...	11·4	2·3	15·6	2·8	13·4	1·8
Schizophrenics	1·4	1·0	4·2	1·8	2·6	1·0

* S.D. = Standard deviation of percentage in preceding column. The figure given in brackets under the name of the group is the statistical size of the group for the purpose of estimating the incidence of manic-depressives in the group.

It is necessary to note that the figure given in brackets under the name of the group, indicating its size for estimating the percentage of manic-depressives, does not represent its real size, or its statistical size for the estimation of the frequency of other abnormalities. For instance, the number of children of Group I was 269. For the purpose of estimating the frequency of "cycloid psychopaths" I have reckoned only those over 20 years of age, 193 in number. For the estimation of the frequency of schizophrenia, those between the ages of 20 and 40 were counted only in part, according to the principle I have already described for the estimation of manic-depressives, but giving in this case a population of 146 persons; while for manic-depressives themselves the figure is further reduced to 116. It is with some hesitation that I have used the term "cycloid psychopath." Under it I have included all persons who have shown well-marked swings of mood lasting considerable periods, varying from over-activity and elation to inertia and depression, or varying from normal in one of these directions only, or persons of a permanently depressed or boisterous overactive temperament, these abnormalities of mood being so marked as to be frankly obvious to friends or relatives, but not being so extreme as to lead to illness or temporary or permanent incapacity. In the latter event I have included such persons among the psychotics, using therefore a purely social criterion as to what shall necessitate a diagnosis of manic-depressive insanity—that of social incapacity of such a degree that it has necessitated medical treatment.

It will be seen that this investigation fails in several particulars to fill the requirements which I gave earlier in the paper. It cannot be claimed that thoroughly adequate information has been obtained about all the persons investigated. Their number is really inadequate to base any certain figures on my findings. It is on this account that I have given the standard deviation of all the percentages. It is generally assumed that the true figure will lie within the limits given by the observed figure, plus or minus twice its standard deviation. Thus the frequency of manic-depressives among the children of Group I was probably between $15{\cdot}5 \pm 2 \times 3{\cdot}4\%$, i.e. between 8·7% and 22·3%. Such a large possible margin of error indicates the rather unsatisfactory character of this type of investigation. Further points of possible criticism are that my diagnosis of manic-depressive insanity in parents and children might well be questioned in many cases by competent psychiatrists, usually

on the grounds of insufficiency of information. To this the only reply is that to class such persons statistically under such titles as "mental illness, of unknown nature, but with affective features" would hardly make informative reading, and that it is sufficient if one accepts the figures with the proviso that in a high proportion of cases the diagnosis has not been certainly established. Finally, it cannot be claimed for this work that the statistical working out is free from all source of objection.

In discussing what conclusions one might draw from this investigation it is necessary to underline these points. The inadequacy of material, its insufficient ascertainment and not irreproachable working out have not prevented previous authors from putting forward complicated theories of the genetic basis of manic-depressive insanity. Hoffmann has built up a theory involving three independent genetic factors, each as it were carrying different weights, and a total weight being necessary to precipitate the individual into a psychosis, a lesser weight being sufficient to make him a cycloid or cyclothymic personality. Rosanoff, Handy, and Plessett (1935), in their study of manic-depressive twins, propose a theory involving two independent factors, a cyclothymic autosomal factor and an activating factor in the x-chromosome, both factors being dominant. Rüdin proposes a theory involving one autosomal dominant and two autosomal recessives. Luxenburger favours a similar theory with one recessive and one dominant. From our present knowledge it would appear that all these theories are quite premature. Such speculations may certainly be possible, but are improbable, unsupported by any real evidence and serve no useful purpose.

In our knowledge of the genetics of manic-depressive insanity only two things stand out as fairly certainly established, firstly that it is inheritable, and secondly that the inheritance follows a dominant type. The simplest possible theory to account for the facts is that the inheritance depends on a single dominant autosomal gene. Once dominance is assumed, this theory must be shown to be inadequate before any other is even provisionally accepted. There are not sufficient facts at present to reject this theory.

On this theory the expectation of manic-depressives among the parents, brothers and sisters and children of manic-depressives would be 50%. Luxenburger gives the percentage of manic-depressive insanity among the parents and siblings as 10·6 and 12·6%. For the children he uses Hoffmann's figures, which I think must be rejected. I have found corresponding figures to Luxenburger's, though slightly larger, for parents and children. They are all far below the 50% level, a fact which is usually held to be sufficient for the rejection of a theory of simple dominance. There are however many reasons why the figures actually found should be so much below theoretical expectation. No genetic factor works in the void, but in an environment which may help or hinder its expression. Rosanoff and his co-workers found that only 70% of the probably uniovular twins of manic-depressives themselves developed the illness. This gives us a direct measure of the influence of the environment, and at the same time reduces the theoretical expectation of 50% to 35%. A large part of the remaining difference may well be accounted for by the very serious difficulties of ascertainment, and to the probability that many persons who have true depressive psychoses are not sufficiently severely or sufficiently long ill to require even perhaps the advice of a doctor, still less incarceration in a mental hospital or psychiatric clinic. There are however theoretical grounds which make it probable that a part also of the difference between theory and expectation is itself genetically determined. These genetic influences are conveniently included under the term "genotypic milieu."

The gene or genes responsible for the appearance of any character have to work not only in an external environment, which as Rosanoff's work has shown, may have a very large influence, but also in the internal environment of all the other

genes which go to make up the hereditary structure of the individual. This genotypic milieu is the same for both individuals in the case of uniovular twins, and so does not find expression in Rosanoff's figures. That it can be very important is shown by recent work on Drosophila. Timofeeff-Ressovsky (1934) has shown that the recessive gene " vena transversa interrupta," which brings about an interruption in the transverse vein, shows itself normally in homozygotic culture in only 1 to 5% of the flies, all of whom should exhibit the change. This percentage is raised to 40 to 100% if a second recessive gene is present also homozygotically, which by itself has no effect on the transverse vein, but shortens one of the longitudinal veins. This is a good example of a " weak " gene, and weak genes are so common, that in spite of difficulties of investigation in their case, they are already held to be more frequent than the " strong " ones. Timofeeff remarks that it is absurd to speak of one gene as being the only one affecting a given change. Every single gene known in Drosophila can be shown to have an influence on several different qualities; and there is no change which is not affected by several different genes. In any single quality one is not dealing with a single gene, but with the totality of genes. Dominance and recessivity are not absolute but quantitative characters. All genes can be ranged on a scale passing from almost complete recessivity to almost complete dominance, and on quite another scale passing from very bad to very good manifestation. The two scales are not, however, related, and weakly manifesting dominant genes are very common.

These considerations are important for human genetics. It seems possible that we are dealing in manic-depressive insanity with just such a weak dominant gene, that manifests itself in only a proportion of its carriers. To say that the degree of manifestation of such a weakly dominant manic-depressive factor is also affected by other genetic factors, is an entirely different thing from saying that manic-depressive insanity is governed by two or three or more separate factors. The latter is a statement that the psychosis does not appear without all the factors being present, when 100% manifestation results. It seems quite possible that only one gene is responsible for the change, but the degree to which it manifests itself will be governed by a variety of circumstances, genetic and environmental.

In manic-depressive insanity besides the genetic and the purely external environment, there is the environment represented by the body itself. It is a remarkable fact that women tend to develop manic-depressive insanity more frequently than men. Some authorities have tried to explain this by the assumption of a factor in the x-chromosome. Unsupported by accessory hypotheses, this theory does not fit the facts. It seems more likely that the female constitution, involving among other things quite a different endocrine balance, forms a more suitable medium of expression for this particular hereditary factor.

There are, however, other criticisms of a theory of simple dominance. How on this basis are we to explain the bewildering variety of clinical syndromes? In the present state of our knowledge this criticism has no weight. Apart from the predominant mood change, we have no idea what are the primary and what the secondary and inessential features of this illness. The great symptomatic variety is likely to be caused in part by the inclusion of what are not really manic-depressive psychoses. Further, it is probable that in such a condition, in which the whole psyche is involved, many of the varying features are due to other qualities of temperament and character, which are conditioned by other and independent genetic factors. There is no convincing clinical reason for rejecting the theory of one single factor, as the main one responsible for this type of psychic breakdown.

There is one curious fact which is in favour of a theory of simple dominance. It is a remarkable fact that parents, siblings, and children all show about the same percentage of manic-depressives, namely in the neighbourhood of 15%. I can

imagine no other theory which would give this relation, which is just what one would expect on a theory of simple dominance. Furthermore Banse's figure for cousins, given in his paper as 3½% (corrected by Luxenburger to 2·7%) is just about one-quarter of the empirical expectation for parents, sibs and children, a figure that also fits in well with this theory.

Before leaving this aspect of the subject, there is an important observation to make. Geneticists have shown that in the majority of known heritable abnormalities, of Drosophila for instance, the same change may be brought about by a number of quite different and independent genetic factors. Similarly in man it has been shown that there are a number of different genetic types of syndactyly, polydactyly, &c. It may well be that the same holds for manic-depressive insanity. All that I would assert at present is that in the typical recurrent manic-depressives there is sufficient evidence to believe that this is governed in the majority of cases by a dominant type of inheritance, and that there is insufficient evidence to show that the hypothesis of a single dominant autosomal factor as the main responsible agent is insufficient.

Any theory of the inheritance of manic-depressive insanity must take into account the problem of its relationship to schizophrenia. In the children of Groups I and II together, there was 2·6% of schizophrenics (in the total of all the children there was about 6%). This is a very high figure, as all that one can expect, were manic-depressive insanity to have no relation to schizophrenia, is about 0·85%. In the German literature, the matter is usually represented as just the opposite. Luxenburger gives the liability of sibs of manic-depressives to schizophrenia as 0·9%, less than that of the general population. These figures are based on Rüdin's work, and require confirmation. Similarly Luxenburger gives the probability of children of manic-depressives developing schizophrenia as nil. This is based on Hoffmann's work, who omits to state in his statistical analysis that he found among his 162 children five cases of schizophrenia. On further partial examination and catamnesis on this material two more cases of schizophrenia have been discovered, raising the percentage of schizophrenics among these children to over 4%. In previous years Krauss (1903) found among the children of cyclic parents schizophrenic more frequently than cyclic children. Luther (1914) found among the children of manic-depressives as many other psychoses as manic-depressive ones, and most of these other psychoses were schizophrenic. Smith (1925) found that in cyclic-schizophrenic crossings, schizophrenic children were commoner than in crossings between normals and schizophrenics. All these findings point to a special relation between manic-depressive insanity and schizophrenia, which is supported by my finding of 2·6% of schizophrenics among my children, when all possible incorrect diagnoses had been eliminated. This figure is of no great statistical significance; yet I am inclined to believe that it represents a real tendency.

In attempting to explain this finding one might be led to examine the family trees of these cases to see whether schizophrenia appeared in other members of the patient's family and perhaps of the family into which he married. Of the fifteen families in which manic-depressive subjects had schizophrenic children, in ten cases I could find no other schizophrenic in either the patient's family or in that of the husband or wife. In one case the patient had married into a family with a schizophrenic member, in the other four cases there was schizophrenia already in the patient's own family. I do not think that these findings, even if they had been much more positive, could give any explanation of why manic-depressives should have more schizophrenic children than normal parents do.

It seems established that manic-depressives are scarcer than might be expected among the relatives of schizophrenics, so that the positive correlation, if it exists, is in one direction only. It is this sort of finding that has led some authorities to an acceptance of the now somewhat discredited theory of anticipation. Others would

explain the relationship between manic-depressive insanity and schizophrenia by holding that both are due to a general neuropathic tendency. Others again would endorse the theory that both manic-depressives and schizophrenic psychoses are dependent on two or more genes and have one or more of these in common, that there is in fact a common hereditary factor. The facts, however, particularly the one-sidedness of the relationship between the two psychoses, would not appear to support any of these theories.

Manic-depressive insanity, however, does not stand alone in this peculiar relation to schizophrenia. The relatives of general paralytics and epileptics also show an increased incidence of schizophrenia, and it would seem undesirable to assume the presence of common hereditary factors in each and all of these cases. A more plausible explanation would lie in alteration of the capacity of manifestation. It would not seem improbable that the carrier of any hereditary factor which shows itself in disturbance of the psyche will not only be more predisposed to that special kind of disturbance, but also to the more profound and destructive disturbance of schizophrenia, or in other words that the gene or genes responsible for the development of schizophrenia find it easier to manifest themselves in a genotypic milieu, which includes other hereditary factors which predispose to psychic disorder, such as manic-depressive ones, whether those other factors have actually manifested themselves or not.

One is tempted to take this possible explanation further and make the following suggestion. There is in genetics no very hard and fast line between dominance and recessivity. This quality also of the gene frequently depends on environmental factors as well as on the genotypic milieu. It seems quite possible that the presence of a manic-depressive gene might, when present in the same individual, have the effect of lending the schizophrenic gene a semi-dominance, so that this might manifest itself in a heterozygotic individual. It is conceivable that some process like this is responsible for the strange atypical psychoses half way between manic-depressive psychoses and schizophrenia in symptomatology and course, which as a matter of clinical experience are not infrequently seen. I should hesitate very much to advance this sort of speculation, but that there is a way in which it could be tested. If the manic-depressive gene does have any activating influence on the schizophrenic factors, then one would expect the majority of the schizophrenic children of manic-depressives to be themselves masked manic-depressives. An investigation of their children would then show the reappearance of manic-depressive insanity. In my material I have five cases where something is known both of the generation preceding and of that following a case of schizophrenia appearing in a manic-depressive family, and in one of these that is the case. Here the patient, a woman, had a perfectly typical recurrent manic-depressive psychosis, with complete recovery after the attacks. Her mother had, at the age of 34, an acute psychotic illness with many manic features. From this, however, she never recovered. She developed a chronic hallucinosis with many paranoid ideas and passed at last into a chronic schizophrenic state in which she remained until she died at the age of 79. Her mother, the patient's maternal grandmother, was at various times in her life four times in a mental hospital with recurrent melancholia, and her mother, the patient's great-grandmother, also had one or more psychotic illnesses, of which no details can be obtained. One sees here four generations showing the typical dominant type of inheritance, with a schizophrenic suddenly appearing in the middle, but capable herself of continuing the manic-depressive line. Research on this point might well bear fruitful results.

Many explanations have been advanced for the occurrence of atypical endogenous psychoses, having some of the features of schizophrenia, and others more manic-depressive in nature. Many authors recognize no hard and fast boundary line between these two principal types, but speak also of remitting schizophrenic

psychoses which fail to show any destruction of the personality, and chronic psychoses, manic-depressive in symptomatology, which do. It seems premature to suggest any genetic explanation of these phenomena which will require a fuller clinical study and analysis. It has been suggested that they are due to the concurrent presence in the same individual of both manic-depressive and schizophrenic hereditary factors, drawn in part separately from paternal and maternal sides. My material does not very strongly support this view, and cases of these unusual kinds appear in some of my families where a manic-depressive taint is the only one apparent. Another explanation is that a schizophrenic psychosis appearing in a person constitutionally of the pyknic and cyclothymic type will tend to show manic-depressive features, particularly relatively good preservation of the affect. It would seem likely that in some cases one of these explanations may be the true one, and in others the other; and further likely that some of these atypical psychoses are peculiar in themselves and are due to quite different genetic factors from those of the manic-depressive and schizophrenic psychoses, that they may in fact be found to breed true. Some families published by Leonhard (1934) are especially suggestive of this possibility.

This is a fundamentally opposed attitude to that of Bleuler, who thinks that the qualities of being schizoid and cycloid appear in every normal man in varying proportions, and are so to speak functional antagonists. This view-point would be of little help in genetic research, and likely to lead only to such pieces of research as Hoffmann's. What facts we have seem to be against the view that there are an infinite series of gradations between the normal and the psychotic, and if English psychiatrists adopt this view, they should be clear on what grounds they do so.

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