# The Genetics of Depressive Behaviour

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CHAPTER IV

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## Introduction

Family studies of affective disorders have recently been reported from America, England, Norway, Sweden, Denmark, Switzerland and Japan. What questions have they been trying to answer? Probably the three main ones can be stated briefly as follows:

How much is inherited?
How is it transmitted?
How can it be subdivided?

Considering the very diverse populations from which the answers have been derived, they are in remarkably good agreement. They are also largely in agreement with the very extensive investigations carried out before the war, mainly in Germany, and on the whole they can be said to extend rather than reverse the findings of those days.

I also want to discuss a rather different sort of question; namely,

Why is it inherited?

Although this question has no answer, it is possible that some practical result may follow from trying to provide one. I shall discuss two hypotheses based on observations of animal behaviour which may help to direct attention to a promising field of enquiry.

## Part I.

### Family Studies of Affective Disorders

*How Much is Inherited?*

A comparison of the concordance rates for monozygotic (MZ) and dizygotic (DZ) twins still provides the most efficient method of calculating the relative importance of heredity on the one hand and environmental or random factors on the other. Seven sytematic series have been reported so far, and the main findings are presented in Table I. The running total is now quite large at 97 MZ and 119 DZ pairs. The concordance rates of 68 per cent. and 23 per cent. are clearly quite different, and indicate an important genetic effect.

The earlier studies may have contained a large number of severe cases, and it is interesting to see that the latest Danish survey, based on

Table I

*Concordance for Manic-Depressive Psychosis in Seven Twin Investigations*

| Author | Monozygotic pairs | | Same-sexed dizygotic pairs | |
|---|---|---|---|---|
| | Concordant | Total | Concordant | Total |
| Luxenburger (41) .. .. .. | 3 | 4 | 0 | 5 |
| Rosanoff (59) .. .. .. .. | 16 | 23 | 8 | 35 |
| Kallmann (31) .. .. .. .. | 22 | 23 | Not stated | |
| Slater (66) .. .. .. .. | 4 | 8 | 3 | 15 |
| da Fonseca (18) .. .. .. | 15 | 21 | 15 | 39 |
| Essen-Möller (14) .. .. .. | 1 | 8 | 0 | 3 |
| Harvald and Hauge (25) .. .. | 5 | 10 | 1 | 22 |
| Total .. .. .. .. .. | 66 | 97 | 27 | 119 |
| % Concordant .. .. .. .. | | 68 | | 23 |

all the twins born in a certain period, gives much the same result. In fact, although there may be an overall relation between severity and concordance, this does not apply to individual cases. Slater's Case 105 was very probably monozygotic; the proband had over 20 severe bouts of mania and depression between the age of 28 and follow-up at age 64, whereas her cotwin, although of very similar temperament, reported no abnormal mood variations at all. Rosanoff gives a very similar case report. Thus there is no certain genetic determination, and even if they were corrected for age the concordance rates in Table I would not reach 100 per cent. This point emerges clearly from an analysis by Dr. K. Abe of the relation between concordance and the time elapsing since the onset of the illness in the first twin (Fig. 1). It is interesting to see from the figure that the relation is exponential, and that the affective disorder group does not show the dip just after the onset in the first twin which is apparent in the schizophrenic group.

The concordance for DZ twins would, with age correction, be rather above the usual rate for same-sexed siblings. This may be due to the greater similarity of environment for DZ twins, or it may result from the fact that they were investigated more thoroughly than siblings usually are.

The morbidity risk for first degree relatives is usually found to be between 10 and 15 per cent., which is well above the population figure. This supports the data from twins, although on its own it could equally well be explained by some form of cultural transmission. In fact Wilson (74) has made a case for transmission by a family tradition of pressure to social conformity.

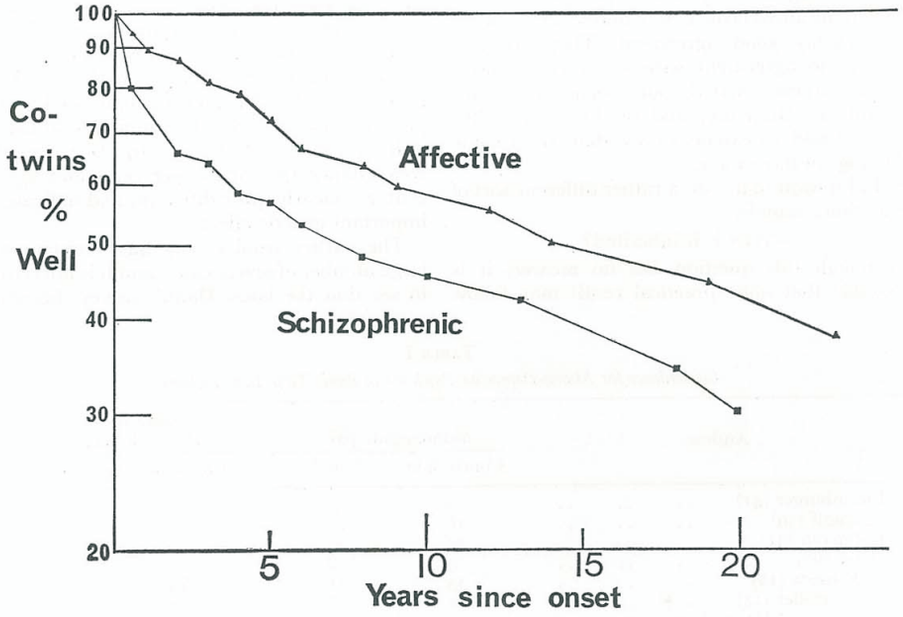


FIG. 1.

Proportion of MZ cotwins remaining well up to 23 years after onset of illness in first twin (adjusted for dropouts due to death, etc.). Analysis by Dr. K. Abe of data from the Maudsley twin series; affective groups contains 39 pairs.



It is possible that the higher concordance of MZ twins is due to the fact that environmental influences tend to be more similar for MZ than for DZ twins. Because of this, the case histories of pairs of MZ twins reared apart are of particular interest, and in the Appendix I have gathered all those I could find in which one or both twins has suffered some form of affective disorder. Eight of the twelve pairs are concordant, which is much the same figure as for the twins reared together; although it is possible that for the rather milder illnesses which some of these twins had the DZ concordance rate might be higher, and therefore the MZ/DZ difference might be less.

*Does the Family Risk Vary?*

This question is important for theoretical reasons, and for the control of bias in comparisons between different groups. Clouston, who with Mott and Maudsley constituted the early English school of psychiatric genetics, asserted (10) that heredity was strongest in those cases exhibiting undue mental exaltation and excitement, and weakest in those who became ill in old age. Several recent authors have addressed themselves to these problems.

There is good agreement that the family risk is higher when the proband has *mania*, whether or not he has depression too (3, 4, 53). Angst (3) made the interesting observation that in the families of his patients who had had manic attacks the secondary cases were distributed evenly between the sexes, whereas in the families of pure depressives there was a preponderance of female cases.

Using as a criterion the diagnosis of *involutional melancholia*, Kallmann (31) found a lower concordance in MZ twins and Stenstedt (70) a lower risk in parents and siblings, as compared with the main body of endogenous affective disorders. Using age itself as the variable, and dichotomizing at about 50, several authors found a lower family risk in their late onset cases (3, 28, 34, 35, 77). There have been one or two exceptions. Stenstedt (69) found no difference with a dichotomy at age 50, but it must be remembered that his involutional cases were excluded from this material. In their cases over 50, Woodruff *et al.* (77) were not able to show any difference in age at onset between those with and those without a positive family history. The same group (75) found no difference in morbid risk between the sibs of the early onset and late onset cases, and they attribute the higher risk for parents of the early onset cases to more complete reporting, the late onset cases being older and with presumably fewer informants from the parental generation. It is also possible that this age difference obscured a real difference in morbidity risk in the siblings, the siblings of the early onset cases being younger and not having passed through so much of the risk period. The abridged Weinberg method, which was used with a risk period of 20 to 80, is not really sensitive enough to compensate for the age differences, and in fact practically none of the siblings had completed the risk period. On the other hand, it has been pointed out to me by Dr. K. Abe that there may in such cases be an underestimate of the morbidity risk of the relatives of the late onset cases, due to the familial correlation in age at onset; the risk period for these relatives is later, and in order to make a comparison between the two groups it would be necessary to use the Strömgren method with a different set of weights for each group. Not only is this the case, but the greater mortality during the later risk period may lead to an underestimate of the mean age of onset of the relatives of the late onset cases. A further difficulty in comparing groups who have had a different number of attacks, also pointed out by Dr. Abe, is that the history tends to be taken by a fresh doctor for each attack, possibly from different family members, so that the ascertainment of familial illness is likely to improve with each attack. Until these methodological difficulties are resolved, it seems reasonable to conclude on balance that the genetic component is less in the depressions which start in later life. So far as we can tell, it is a steady decline, and the fall stops short of zero.

As might be expected, the presence of *precipitating factors* is associated with a low family risk (19). Stenstedt (69) found only half the risk in his cases with somatic or psychological precipitants (those with deviant personality and atypical clinical features were also included). In his later study of neurotic

depression (71), in which exogenous factors were nearly universal, Stenstedt found that the family risk was only just greater than the risk in the general population.

The one embarrassing feature about this field of enquiry is that it is extremely difficult to provide evidence that the family risk increases with the *severity of the illness*. Of course, all the recent work has been on in-patients, which presupposes a certain severity. The only investigation of out-patients was reported by Paskind (50) and the family risk was much the same as that reported in the same country for hospital cases; he later reported (51) that in the 69 cases where both parents were affected the attacks were longer and the intervals shorter. Asano (4) found a higher family risk with more attacks and longer attacks, but others have been unable to find any relation with number of attacks (69, 77). In fact, the latter authors made a careful comparison of their cases with and without a positive family history, and were unable to detect any difference between the two groups.

In general, it seems to be the case that the family risk is highest with the classical type of manic-depressive psychosis, and that it tends to fall slightly when the clinical picture deviates from this in any direction.

*Mode of Inheritance*

There are two main issues here. First, are major genes involved, or is the tendency to affective disorders a quantitative trait determined by innumerable genes? Secondly, to what extent are the same gene or genes responsible for all cases of affective disorder; in other words, how much of the genetic determination is heterogeneous?

The major gene hypothesis was presented by Slater (65) in its most economical form of a dominant gene with incomplete penetrance (about a third of the carriers would be affected). Simple recessive inheritance is ruled out by the equal risk in parents and siblings, and if rare recessives were making any significant contribution we should expect an excess of cousin marriages. Sex-linked inheritance is excluded because both parents transmit the disease equally to both sons and daughters. More complex genetic models have been put forward (e.g. 5), but they do not appear to have any heuristic advantage over the simple one. Unfortunately, all the genetic variance cannot be explained by the single dominant gene, which makes it necessary to postulate modifying genes, and thus the distinction between major gene and polygenic models becomes blurred.

Nevertheless, important advances have been made towards distinguishing between the two theories (13, 46, 67). Edwards (13) has calculated the expected morbidity in various degrees of relatives according to polygenic theory. In first degree relatives the expectation is the square root of the population risk, so that for a population risk of 1 per cent. the expectation in the relatives is 10 per cent. This is within the range of actual findings, and it is necessary to estimate the risk in more distant relatives in order to obtain a differential prediction: the expected risk falls more rapidly with polygenic than with major gene inheritance. Unfortunately it is difficult to get a reliable figure for distant relatives. Ødegaard (47) found risks of 12·4 per cent., 5·2 per cent. and 5·3 per cent. for first, second and third degree relatives respectively (of manic-depressive probands), the actual number of secondary cases in each group being 19, 17 and 22 (the general population risk was about 2·7 per cent.). Here the risk for first degree relatives is rather low for polygenic theory, and the risk for third degree relatives rather on the high side for any theory. In the case of the children of two affected parents the risk is higher on polygenic than on monogenic theory; but the difference is not great, and the obstacles in the way of collecting sufficient reliable data on such families (40) renders them of little use for the present purpose.

Slater (67) has investigated the expectation that, on single gene theory, the secondary cases among the ancestors would be expected to occur either on the mother's or on the father's side rather than to be distributed between the two stocks. Calculating the predictions to be made from single gene and polygenic theory, he made the unexpected finding that the predictions are really rather similar, and in order to obtain a differential prediction it is necessary to study families in which there are three or more cases in the ancestry, or to go back to the grandparental



generation. This information as usually obtained is not very reliable, and is liable to be biased to one side of the family or the other, depending on the source of the family history. But it may be that suitable data will be provided from one of the Scandinavian countries where central statistics of hospital admissions are kept, and where it is possible to trace a patient's ancestry more easily than it is in England.

The demonstration of linkage with one of the many marker genes would provide good evidence of major gene transmission. This would present a formidable task, and it is not surprising that no work on the subject has appeared. Because of crossing over, there may be several relatively independent linkage groups on each chromosome, so that the chances of finding a marker in the same group might not be great. Moreover, in combining the data from more than one family, one would be making the assumption of genetic homogeneity. Very close association between a marker gene and the disease would also be evidence for a major gene effect, but such a finding would be very unlikely; it is not the case for atypical serum cholinesterase (33) or for isoniazid acetylation (55), and in spite of a recent claim for an association with blood group A (49) extensive previous investigations have failed to show any association between mental illness and the ABO, MN or Rhesus groups.

A major gene could also be detected by the demonstration of a bimodal distribution for some trait in first degree relatives. To find such a characteristic of the carrier state, the optimum comparison would be between unaffected MZ cotwins of patients and more distant relatives. No attempts to precipitate affective disturbance in hypothetical carriers have been reported, and such a procedure might be liable to ethical objections. In the case of schizophrenic disorders, Anastasopoulos and Photiades (2) claim to have produced a typically dominant form of pedigree with the aid of LSD.

According to the dominant gene theory, one of the parents must be a carrier, even if unaffected; therefore the risk for siblings should not depend on whether a parent is affected; in fact, the risk for siblings of a patient appears to be higher when one parent is also affected (69, 75). This is what one would expect according to polygenic theory. Of course, it is possible to argue that when a parent is affected there is a lack of favourable modifying genes in the family, and this demonstrates the inevitable blurring of predictions which the postulation of modifying genes is bound to introduce.

Nevertheless, it can be seen from the above discussion that the dominant gene theory is heuristically valuable, its predictive power being greater than with either the polygenic model or any of the more complex genetic theories.

*Subdivisions of Affective Disorders*

The problem of classification is discussed at length in Chapter II of this symposium, but it is of interest to consider what light the genetic evidence throws on this problem. We have already seen that the degree of family risk varies with certain features of the illness, but that the variation has not been shown to be discontinuous and is not of sufficient degree to call for a subdivision on its own account. In the following discussion we shall be concerned with qualitative similarities between members of the same family. If a clinical feature, or group of features, breeds true and is present in most of those family members who develop the illness, then this is a strong ground for saying that it has a specific genetic determination.

*Involutional Melancholia*

Two important investigations have shown that the relatives of patients with involutional melancholia tend to have affective illnesses indistinguishable from the main body of affective illness. Stenstedt (70) studied 307 cases, a large population, and there were 44 secondary cases of endogenous affective illness. Twenty-six received diagnoses of involutional melancholia (higher than expected by chance), but the remaining 18 were diagnosed as manic-depressive psychosis. Three of them began under the age of 20. The mean age of onset of the secondary cases is shown in Table II, and it can be seen to be half way between those of involutional and manic-depressive probands. Kay (34) divided his late onset cases at age 60, and found that the majority of the secondary cases in both groups started before the age of 50.

TABLE II

*Mean Age at Onset of First Affective Disorder*
Stenstedt (69, 70)

| | years |
|---|---|
| Probands with involutional melancholia .. | 57·5 |
| Parents and siblings of above .. .. | 48·2 |
| Probands with endogenous depression .. | 38·7 |

Thus although the age dimension is an important genetic variable, there is no evidence for a dichotomy along it. In late onset cases we can expect the family risk to be lower, the secondary cases to be more heterogeneous, including an excess of schizophrenia (31, 34). Slater (66) found a correlation for age at onset of +0·35 for 60 pairs of first degree relatives, and Stenstedt's figure is not far from this.

*Neurotic, Reactive or Symptomatic Depression*

It is not unlikely that of the increasing number of depressions now coming for treatment many are not genetically predisposed, and that their presence complicates the genetic analysis of those who are. Thus it would be very useful from the genetic point of view to split off the reactive depressions and concentrate on the endogenous cases. This distinction is, of course, more important for single gene theory than for a polygenic system, as the reactive cases would not be gene carriers. According to polygenic theory, the endogenous cases would merge imperceptibly into the reactive, but it would still be very advantageous to have an endogenous/reactive dimension according to which the probands could be rated.

Unfortunately, the genetic findings have not been very promising. Stenstedt (71) studied 176 cases of neurotic depression and found that their families were closely interwoven with his manic-depressive families: he remarks on the great difficulty of distinguishing the two conditions in a genetic investigation.

Winokur and Pitts (76) studied 75 patients admitted to hospital with a diagnosis of depressive reaction, in the hope of comparing their family histories with those of manic-depressive cases. Unfortunately, there was diagnostic agreement about only 12 of the cases, and the families of the 45 who were finally diagnosed as manic-depressive did not differ from the main body of affective disorders. The same group (77) also took their cases of endogenous depression over the age of 50 and divided them into two groups, 68 with a family history of affective disorder and 98 without: they compared the groups on a number of clinical items but could find no difference between them.

Ödegaard (47) had used the same method, taking all psychotic cases but comparing those with no affected family members with those who had at least four affected relatives: he found no difference, although the significance for affective disorders is not great because the numbers in these categories were small. In his whole material, he found that neurosis was as common in the families of manic-depressives as in those of reactive depressions, but that of all the psychoses "manic-depressive psychosis comes most closely to being a genetical entity". Of the 49 psychotic relatives of manic-depressive probands, 24 were manic-depressive, and only 14 had reactive depression.

Shields and Slater (64) have reported twin data on neurotic depression. These were same-sexed twins who had received a diagnosis of some sort of neurosis at the Maudsley Hospital; they were rediagnosed by Slater independently from case summaries. In Table III are presented those probands who were given an independent diagnosis of 314, and those with 310 are added for comparison. It can be seen that whereas the

TABLE III

*Diagnoses of Cotwins of Maudsley Same-Sex Twin Probands who have received a Hospital Diagnosis of Neurosis or Personality Disorder and who received an independent Diagnosis of Anxiety Reaction 310 or Depressive Reaction 314. Cotwins also diagnosed independently from Case Summaries. In two Pairs both Twins are counted as Probands (310/310 and 310/314). Breakdown of Data in Shields and Slater (64) by kind Permission of the Authors*

| Probands | | | Diagnoses of cotwins | | | | | |
|---|---|---|---|---|---|---|---|---|
| Diagnosis | MZ or DZ | N | 300 | 301 | 310 | 314 | Other | Normal |
| 310 | MZ | 17 | | | 7 | | 1 | 9 |
| | DZ | 28 | | 1 | 1 | 2 | 1 | 23 |
| 314 | MZ | 8 | | | | | 3 | 5 |
| | DZ | 16 | 1 | 1 | 1 | | 1 | 12 |



probands with anxiety states tend to have twin partners with anxiety states, in the case of neurotic depression there is no concordance for diagnosis. Three of the MZ twin partners had diagnoses of personality disorder, and the DZ partners were of diverse diagnosis. As far as these small numbers go, they tend to suggest that 314 is not a specific genetic entity.

Thus it has not proved possible to make a clear genetic distinction between one kind of depression and another. If there are non-genetic depressions masquerading as endogenous cases, they are extremely clever phenocopies. However, it may be that the next advance will come from clinical diagnostic studies, and with improved methods therefrom the geneticists will have more success; or even better, the two approaches could be combined.

*Bipolar Psychosis*

If we turn from depressions to those cases that exhibit swings of mood in both directions, we have distinctly more promising findings to report. Of course, in its 114 years of history, the entity of bipolar psychosis, or folie circulaire, or cyclothymia, or classical manic-depressive psychosis has had a rather chequered history. When it first fell into disfavour, the attempts to revive it in the last decade of the nineteenth century were described by MacCurdy as "attempts to build an edifice on shifting sands"; and he pointed out that one of the reasons why Kraepelin combined it with the remainder of affective psychoses was that all types of cases were to be found in the same families. Nevertheless, we must not prejudge the issue. The importance of classifying the bipolar affective psychoses separately has been emphasized by Leonhard (37), and a recent investigation in Sweden by Perris (53) gives strong support to Leonhard's position.

Perris studied 138 cases who had had at least one attack of depression and one of mania; a manic swing following treatment for depression was included provided it was of sufficient intensity to require changing medication from anti-depressive to sedative. He compared them with 139 cases who had had at least three discrete attacks of depression, selected randomly from hospital admissions over the same period as the bipolar cases. The follow-up was of the high standard to which we are accustomed in Scandinavian work. The patients were interviewed by the author, and the relatives by the Community Service psychiatric nurses. A large amount of corroborative evidence was collected from various records.

The results were quite striking. In the families of the bipolar patients, the expectation of bipolar psychosis was 10·1 per cent., but the expectation of unipolar psychosis was not increased at all. The unipolar patients were defined as having had three discrete attacks of depression; the expectation of bipolar psychosis among their relatives was not increased (0·3 per cent.), whereas the expectation of three or more attacks of depressive psychosis was 5·0 per cent. with an additional expectation of 1·4 per cent. for two attacks of depression. The actual numbers of relatives in each category are set out in Table IV, where the marked difference between the two conditions can readily be seen. The picture is a little complicated by the large number of suicides, and by the cases who have only had one attack of depression, or who are otherwise not classifiable as uni- or bipolar, who appear as "unspecified affective disorder".

This is clearly a very challenging result, and if confirmed will be strong evidence that bipolar and unipolar psychoses are genetically independent entities. The finding will be of

TABLE IV

*Data from Perris (53) Showing that in the Families of Probands with Bipolar Psychosis (Mania and Depression) there is a Great Increase of Bipolar Psychosis and no Increase of Unipolar Depressive Psychosis (Two or More Attacks of Depression without Mania); in the Families of Probands with Three or More Attacks of Depression, there is an Increase of Unipolar Depressive Psychosis but no Increase of Bipolar Psychosis*

| Disease | Number of cases: Relatives of 138 Bipolar probands | Relatives of 139 Unipolar depressive probands |
|---|---|---|
| Bipolar psychosis .. .. | 58 | 2 |
| Unipolar psychosis .. .. | 3 | 44 |
| Unspecified affective disorder | 14 | 16 |
| Suicide .. .. .. | 32 | 24 |

particular significance because it will also be evidence that the bipolar psychoses are mediated by a major gene. It was pointed out earlier that polygenic inheritance could mimic major gene inheritance for common disorders, but here is a relatively rare disorder with a morbidity risk in the first degree relatives (if suicides and unspecified cases are included) of $18 \cdot 1 \pm 1 \cdot 6$ per cent. According to polygenic theory the corresponding population risk should be $3 \cdot 3$ per cent. (the square of the risk in first degree relatives) and this is clearly much too high for bipolar manic-depressive psychosis.

The data provided by Stenstedt (69) do not altogether support the dichotomy. Looking at his second Appendix, and considering only bipolar cases and those who have had three or more attacks of depression, there are seven families who have two affected members. In three families there occur only unipolar depressions, three families contain both bipolar psychosis and unipolar depression, and one family contains two cases of bipolar psychosis. Moreover, whereas Perris found that cases of unipolar mania resembled bipolar psychosis in their family history, Stenstedt's data show that they go with unipolar depressions. In addition to his three families with unipolar depressions only, he has three with unipolar manias only and six which contain both unipolar manias and unipolar depression. There is no family with both bipolar psychosis and unipolar mania.

Nor do the findings of Angst (3) suggest a clear dichotomy. There was no increase in bipolar psychosis in the relatives of his monopolar probands, but there *was* an excess of unipolar depressive psychosis in the relatives of the probands with bipolar psychosis. Perris (page 187) discusses various reasons for the discrepancies between the two investigations.

On the other hand, the data of Slater (66) rather tend to support the Leonhard–Perris dichotomy. Except for one possible recurrent depression in a father on whom information is not complete, the bipolar cases all tend to go with bipolar cases, and the unipolar depressions likewise.

Perris's results are clearly most challenging, and call for repetition on a different population. When this is done, it would certainly be worth while to provide full case histories of the probands and secondary cases. The age of onset, and the duration of, interval between, and sequence of attacks would make good material for detailed comparison. In such a confirmatory study, the families should be investigated "blind". The relation between these and the other bipolar psychoses described by Leonhard (see 37) is a further question of interest. In spite of previous failures to establish this clinical category, the evidence here is strong and based on a large case material; it may be that in limiting his unipolar probands to those who have had three attacks of depression, Perris has managed to unwind a little the tangled skein.

*Atypical Psychosis*

It has been pointed out (37, 45) that certain psychoses with both affective and schizophrenic symptoms tend to breed true rather than to segregate into the "parent" psychoses. Moreover in some cases they tend to be unusually penetrant, as in the family recently reported by Kaij (30) in whom no less than nine members were affected. These reports open up the challenging possibility of being able to break off rare dominant conditions from the main body of affective disorders in the way that rare recessive conditions have been isolated from mental deficiency. Although no specific biochemical syndrome has yet been identified, these families are being subjected to intensive investigation, and suggestive anomalies of EEG and endocrine function have already been noted. Linkage studies would also be appropriate, and might be of great interest to the family members one or two generations hence.

*Resemblance in Individual Features*

We have seen that the relatives of Stenstedt's involutional cases tended to have a relatively late onset. Within his main material, the correlation for *age of onset* between pairs from different generations is $+0 \cdot 29$, not quite significant but similar to the figure of $+0 \cdot 35$ which Slater (66) gives for 60 pairs. As would be expected, these correlations are lower than those found when schizophrenic cases are included.

Of the individual features, both Stenstedt



TABLE V

*Number of First Degree Relatives who have had an Affective Disorder including or not including an Attack of Mania; Probands Classified by the same Criterion. Data of Stenstedt, 1952 (S) and Angst, 1966 (A). T = total.*

| | | Relative mania | | Relative depression only | | % Relative mania |
|---|---|---|---|---|---|---|
| Proband mania | S | 10 | S | 17 | | |
| | A | 7 | A | 18 | | |
| | T | 17 | T | 35 | | 33 |
| Proband depression only | S | 10 | S | 64 | | |
| | A | 1 | A | 20 | | |
| | T | 11 | | 84 | | 12 |

TABLE VI

*Number of Attacks of Affective Disorder in Pairs of First Degree Relatives, taken all Ways. Combined Data of Stenstedt (69) and Slater (66)*

| Younger relative \ Older relative | 1 | 2 | 3 | >4 | Total |
|---|---|---|---|---|---|
| 1 | 35 | 17 | 7 | 10 | 69 |
| 2 | 15 | 4 | 2 | 7 | 28 |
| 3 | 5 | 1 | 0 | 0 | 6 |
| ⩾4 | 8 | 3 | 8 | 26 | 45 |
| Total | 63 | 25 | 17 | 43 | 148 |

and Angst found a resemblance in the presence or absence of *mania* (Table V). The relative is nearly three times as likely to have a manic episode if the proband has had one.

In Table VI can be found the combined data of Stenstedt (69) and Slater (66) for *number of attacks*. An interesting finding seems to emerge: there is a definite resemblance in the occurrence of four or more attacks, while the occurrence of two attacks and perhaps three attacks is related to the occurrence of a single attack. This suggests that if number of attacks is to be dichotomized, the cut should be between three and four rather than between one and two.

Slater (66) also found a family resemblance in the presence of *retardation, anxiety and hypochondriacal preoccupations*; there was no significant resemblance in delusions, hallucinations, depersonalization, agitation or a tendency to suicide or self-injury. Hayes (26) noted a relation between sudden onset in the proband and family history of mania or unprecipitated depression; in his gradual onset cases there was a family history of depression in response to stress such as bereavement.

A family resemblance in *response to treatment* would be of great practical as well as theoretical interest. Pare, Rees and Sainsbury (48) have made a pioneering study in this difficult field, and have produced a little evidence to suggest that response to monamineoxidase inhibitors and to the iminodibenzyl derivatives may be independent familial characteristics. While on the subject of treatment, one should mention that the response to phenelzine may depend on the isoniazid acetylation phenotype of the patient (16).

These different items of resemblance are evidently not independent, and offer scope for some form of multivariate analysis to describe them more economically. It would be interesting to take a large number of pairs of relatives scored on several symptoms and to divide the covariance into "between family" and "within family" components, making a separate multivariate analysis on each matrix. It should be possible in this way to estimate the number of independent dimensions along which family resemblance in symptomatology occurs.

*Relation of Affective Disorders to Other Psychoses*

When the diagnosis of affective disorder is made strictly, remarkably few psychiatric conditions other than affective disorder are found in the first degree relatives. There is, of course, an excess of cyclothymic personalities, which may be regarded as subclinical forms of the disease. Winokur and Pitts (76) found an excess of alcoholism in the males, but very few studies find an excess of neurotic conditions or schizophrenia. This seems remarkable because of the difference in diagnostic customs which Professor Rawnsley pointed out: if everyone is cutting the cake of psychosis into different proportions and still getting a clean cut, the cake must be divided into quite a number of independent segments.

Those studies, on the other hand, which start with all admissions or all psychoses do not get such a clear differentiation. Ödegaard (47)

found some overlap between depressive psychoses and both neurosis and schizophrenia, although of all diagnoses manic-depressive psychosis was the most distinct. Tsuang (72) reported on 71 pairs of sibs who had been admitted to Claybury Hospital, and who had been given independent diagnoses from the case summaries; in 9 cases both were schizophrenic, in 14 both were affective and in 11 cases one was affective and the other schizophrenic. Although the numbers are small, this suggests that like tends to go with like, but that there is a lot of overlap. Tsuang's overlap was greater than that found by Ödegaard and by Mitsuda, and whether this was due to the fact that the diagnoses were from case summaries, or to the fact that they were made independently, is not altogether clear. Mitsuda's conclusion is that typical cases of affective disorder and schizophrenia are genetically distinct, but that the atypical cases of each category overlap; surprisingly he includes epilepsy in his generalization.

All these three investigators tried to find ways of dividing the psychoses to give a better discrimination between categories than is provided by the Kraepelinian types, but, taking single symptoms or groups of symptoms, they were not successful. As Ödegaard remarks, it is not easy to improve on Kraepelin's nosological stroke of genius.

## Part II.

### The Evolution of Depressive Behaviour

Professor Rawnsley has marshalled compelling evidence to show that depression is a common malady. We also know that there is an increased mortality from suicide, probably a reduced fertility (57), and that under primitive conditions the impaired efficiency which it causes must interfere with the rearing of children. Looked at in evolutionary terms, how has this state of affairs come about? We know that we are the result of a selection process the length and ruthlessness of which confound the imagination. How is it that the depressive diathesis has not only arisen, but has failed to be weeded out in the struggle for survival?

Over the last 50 years there have been several suggestions that depressive behaviour performs a useful function (11, 19, 20, 36, 54, 58). Freud (21) suggested that in melancholia there was some process going on in the mind, analogous to mourning, by which the person was able to get over the loss of some loved object. Lewis (39) proposed that depression was an adaptive reaction of the organism to remove it from a noxious environment; it will be recalled that he described "a morbid dissatisfaction with the surroundings" as a feature of depressive illness. It has even been suggested (27) that depression was the natural state of primitive man, but that when his powers of thought evolved to such a level that he was able to contemplate his origins and his future it was necessary for him to evolve our present state of relative elation to enable him to live with his conclusions.

There are, of course, many hypotheses or models which one could put forward to explain the evolution of depressive behaviour. In the last resort they are all untestable. The only use which such models have is to help us to formulate testable hypotheses which we might otherwise not have considered, or bothered to test. This is the only criterion by which such models should be judged; except, of course, that they should have in addition reasonable face validity and fit in with what we know about depressive behaviour. I shall just consider two such hypotheses which I think have a reasonable chance of leading to useful experimental work.

#### *The Hibernation Model*

In 1928 Lange suggested that depression was analogous to hibernation. He pointed out that our environment shows phasic variations, and that we cannot be optimally adapted to each phase. Animals have therefore evolved mechanisms to reduce their activity during phases for which they are less well adapted; sleep, for instance, for that phase of the diurnal cycle for which their vision is poor; hibernation and aestivation for the season of the year to which they are least adapted; and perhaps depression in the case of mankind to keep us huddled in our dwellings when conditions are unfavourable. Exactly what these conditions might have been during evolution, and what factors released the depressive behaviour, we cannot say. It is not difficult to think of possibilities; the seasonal migration of predators, for instance, might have rendered invaluable a temporary mood of pessimistic caution; the death of the first family member would have been a late and cogent indication that the unfavourable season had begun.

There are several practical results from this model. In the first place, it suggests that we should consider the actual behavioural result of the depression; for example, does it make the patient stay at home or does it lead him to go out—does it make him seek company or stay on his own? Although not so useful clinically, these may be biologically meaningful distinctions. Secondly, it makes us look out for naturally occurring events which might be precipitants of depression, although they have no logical meaning for the patient; for example, a flight of birds in a certain direction might signal the advent of a seasonal predator and have become the releasing stimulus for depressive behaviour. The stimulus might not be registered in a conscious way by the patient, and there may be a latent period. Finally, the direct analogy with hibernation should be pursued. There is a small chance that the same neuroendocrine system may be involved in the two types of behaviour, and as yet we have little knowledge of the mechanism of hibernation (44). Animals such as the black bear which "hibernate" without lowering their temperature are even more interesting.

#### *A Dominance Hierarchy Model*

According to this model, depressive behaviour has evolved as part of the complex behaviour which maintains the stability of the dominance hierarchy in social groups. The extensive work of comparative ethologists has made the concept of the dominance hierarchy familiar to us; first described in chickens by Schjelderup-Ebbe (61), and therefore sometimes known as the peck-order, it has been shown to occur in most species of primate (6, 8, 12) particularly in baboons and macaques, who, like man, rely for defence on co-operative aggression rather than escape into the trees. It may well have been a prominent feature of early human society (23) and played a leading part in the evolution both of our intelligence (8) and social behaviour (7). Recently Grant (22) has studied the formation of dominance hierarchies in groups of long-stay psychiatric patients, and has pointed out that such behaviour may be relevant to theories of mental illness.

A dominance hierarchy is essentially an order of precedence and leadership based on individual recognition, and appears to perform the function of allowing aggressive animals to live together in relative peacefulness. Each member knows exactly where he stands in the hierarchy, and if an issue arises between two members the junior submits before a fight occurs.

The behaviour associated with the hierarchy has various affective tones. Aggression and irritability characterize behaviour to subordinates, who are constantly reminded of their position by acts of minor threat and provocation, such as the direct gaze. The subordinate responds with anxiety and withdrawal; he grins or looks away from the direct gaze, gets out of the way when a superior approaches, or presents his hindquarters in a gesture of submission. Thus firm habits of response are built up to each individual in the group. The whole bearing of the animal depends on his position in the hierarchy; at the top there is a relaxed confidence, whereas the animals at the bottom are typically "hen-pecked" and might be said to pass their lives in a state of neurotic depression. The quantity of dominant and submissive behaviour, collectively referred to as "intra-group agonistic behaviour", has been found to be susceptible to experimental manipulation (68).

But however interesting these behaviours of the stable hierarchy may be, they do not help us in the case of phasic states of elation and depression. Here we must look to changes in the hierarchy for our analogy. A change in the order of dominance is a rare event in most species, at least among the males. At such a time there is the possibility of serious fighting and disruption of the group, particularly if two dominant members remain evenly matched for a long period. We might expect that some types of behaviour would have evolved to ensure group stability at such times. Going rather

beyond the ethological evidence, we can suggest that elated behaviour has evolved in connection with a rise in the hierarchy and depressive behaviour in connection with a fall.

The idea that a pathological degree of depression in a "fallen chief" might be of advantage to the group as a whole was first put forward by Rodger (58). He discusses the states which occur in animals, particularly dogs, when they are separated from their masters, and suggests that these could be investigated by ethologists (which is now being done (62)); he then goes on to say: "If we grant that depression is a social biological reaction, then what is its function? Separation from the herd must be a frequent occurrence and it may be favourable to the survival of animal and herd if in this situation the animal reduces motor activity, exploratory behaviour and food intake until an opportunity occurs to rejoin the herd. Here you would have a condition in which anxiety over separation would be accompanied by depressed activity—a state analogous to normal depression.

"But to pursue our speculation a stage further, there may be situations, in the case of animals who have become over-dependent or incapable, in which a more permanent separation is threatened, a male animal, for instance, who has become weakened by age and has been driven out of the herd by younger, fitter males. In such a situation one imagines that there might be a biological mechanism in which, joined to anxiety over separation and depression of activity, there is a loss of those behavioural responses which are designed to lead the individual back to the herd. In psychological terms there would be an acceptance of the herd's rejection. This would be a condition analogous to pathological depression or, more particularly, involutional melancholia. A biological explanation of this kind would serve as a unifying concept embracing clinical, psychoanalytic, social and physiological theories."

*Face Validity*

In Table VII are presented some features of depressive illness against the corresponding features of a fall in the hierarchy. It can be seen that in many cases the behaviour is appropriate to the situation. Perhaps the most important point is that, from what we know of the state of mind of the depressed human being, he is likely to accept his reduced status and not try to fight to regain his former rank. He is not likely to consider himself worthy of it, and if he did he would be pessimistic about the outcome of an attempt to regain it. In such struggles, alliances are important among baboons (24, 78) and macaques (73); and thinking, in his depressed state, that his friends had turned against him, he would be even more dissuaded from fighting.

Thus a depressive behaviour pattern occurring in the animal who is going down the hierarchy, might enable the change to occur smoothly and without endangering the group with fighting and disruption. As far as the group is concerned, the causal sequence is immaterial;

TABLE VII

| Feature of depressive illness | Feature of fall in dominance hierarchy |
|---|---|
| 1. Loss of appetite | Less access to food |
| 2. Loss of libido | Less access to sex outlets |
| 3. Avoids company | Must avoid animals who previously avoided him |
| 4. Ideas of unworthiness and inferiority | More submissive behaviour |
| 5. Selective forgetting of favourable memories | Must forget or forgo well established habits of dominance |
| 6. Average duration six months | Recovery from injury or illness allows resumption of former dominance |
| 7. Commoner in later life | Commoner when powers waning, and more difficult to adjust |
| 8. Commoner in females | Female status varies within harem (often monthly) and between harems |
| 9. Associated with separation and bereavement | May follow loss of allies |
| 10. Increase of anxiety and irritability | Increase of all "dominance hierarchy" behaviour |



the animal may go down because he has become depressed (perhaps perceiving that his position in the hierarchy is untenable) or he may become depressed because he has gone down. The important thing for the group is that when he has gone down he should stay down quietly and not try to make a come-back for some considerable time.

Since these depressive behaviour patterns are advantageous, they should be selected for until the advantage they bestow is balanced by some disadvantage. This disadvantage is likely to be an excess of depressive behaviour, in severity, duration, frequency or in the ease with which it is elicited. Such depression of undue severity, or occurring out of the usual context, would be manifested as depressive illness.

Disturbed behaviour of a depressive type has been reported in baboons (78) and in a macaque (38) in captivity, but not so far in field studies. This is not too damaging to the hypothesis in view of the limited periods of observation which have so far been achieved. Disturbed behaviour of a manic type has been observed in wild baboons by Marais (43); during such behaviour the young males defied the leaders, but no actual rises in the hierarchy occurred. These baboons are reminiscent of some of the manic patients described by MacCurdy (42).

*Predictions*

To what new fields of enquiry does the model lead us, and what testable predictions does it allow us to formulate?

In the first place, we need to know more about the results of changes in dominance hierarchy in macaques and baboons. We must encourage ethologists in the field to make particular note of such occurrences. In the laboratory, it should not be difficult to manipulate the hierarchy experimentally. We know that injections of testosterone can send a low ranking chicken to the top of the peck-order (1), and there is a little evidence that the same may be true of the chimpanzee (9). Pavlov (52) found that castration was a powerful adjunct in the induction of experimental neurosis in the dog, and it may be that the effect was mediated by reducing the animal in the canine hierarchy. We would predict from the model that a baboon artificially lowered in the hierarchy would develop a pattern of behaviour similar to that seen in depressive illness. And it may be (although a species difference is always possible) that the chemical and neurophysiological correlates of such a depressive reaction in the baboon would be similar to those to be found in human depressive illness,

Secondly, we should consider the hierarchical position of our depressive patients. This does not, of course, refer to their social class, but to their standing within their own group of acquaintances. It is possible that a lot of dominance hierarchy behaviour goes on without our being particularly aware of it. Grant has shown that the cues and responses may be very subtle—a glance, a tone of voice, a few degrees of variation in posture. It would, of course, be extremely difficult to test a hypothesis about changes in status as antecedents of depressive attacks. However, it might be possible to observe the effects of variations in status in ward or group therapy situations. Grant was able to observe one change in status made deliberately by the nursing staff, and this resulted in depressive behaviour lasting two or three weeks on the part of the patient whose status was lowered.

Thirdly, regarding treatment, it is worth bearing in mind that prolonged sequences of behaviour are terminated, not by the gratification of a need, but by the performance of some consummatory act (15). What might be the consummatory act of depressive behaviour, and what environmental situation would release it? We know from the researches of Sargant (60) that in primitive societies the milder forms of depression are treated by ritual activities in the group situation. It may be that these ceremonies counteract the tendency to various types of dominance hierarchy behaviour, and it would seem to be worth while studying the effect of such activities, particularly from the point of view of preventing relapses. Several other factors are known to affect the general level of dominance hierarchy behaviour (56), and these could be used in a therapeutic test of the hypothesis.

Finally, it is interesting to reflect that the doctor himself may be perceived by the patient as part of his hierarchical environment. We

know that the overlord of a baboon troop exercises considerable influence over the structure of the hierarchy below him, and that in times of hierarchical uncertainty the junior members are liable to turn to him for reassurance. It may be that a considerable part of a doctor's power to comfort the depressed patient may derive from the fact that he is perceived as high in the hierarchy and at the same time strongly committed to the patient's interests. In long-term psychotherapy, not only does the patient get this prolonged support from an overlord, but, because he has a prolonged exposure to an overlord who is dominant and yet non-threatening, there is time for his submissive reflexes to undergo some extinction. This may also happen in group psychotherapy, where the threats of more dominant members of the group are diverted by the therapist away from the submissive members and on to himself. Thus the dominant members are trained to stand up to the overlord and avoid bullying the submissive members, and the submissive reflexes of the latter, both to the overlord and to the dominant members, are given time to undergo extinction.

## Summary

*Part 1. Family Studies of Affective Disorders*

1. The seven systematic twin investigations so far reported give a total of 97 MZ and 119 DZ pairs. The concordance rates for affective disorder, unadjusted for age, are 68 per cent. and 23 per cent. respectively. Brief case histories are given of twelve MZ pairs brought up apart. The twin data indicate an important contribution from heredity, but that environmental or random factors must also play a significant part.

2. The risk of illness in family members is less in cases of late onset, where there are precipitating factors, and when the clinical picture deviates from the classical form of manic-depressive psychosis. Such differences are not great, and some of the findings are contradictory.

3. Statistical studies have shown that the present family data can be explained by several genetical models, the two simplest being multifactorial inheritance and an incompletely penetrant dominant gene. In either case there may be considerable genetic heterogeneity.

4. Attempts to delineate a genetically distinct entity within the group of affective disorders have not been successful in the case of involutional melancholia and neurotic depression. One Swedish study has shown an almost complete distinction between bipolar cases (having a manic and depressive phase) and unipolar depressive cases (having three or more discrete depressive phases).

5. Although it is possible to select pure cases of affective disorder in whose families the risk of schizophrenia is not increased, when a random sample is taken there is a certain amount of overlap between these categories. By selecting symptoms or groups of symptoms, it has not been possible to improve on the discriminating power of the Kraepelinian dichotomy.

*Part 2. The Evolution of Depressive Behaviour*

6. In depressive states there is an increased mortality from suicide, probably a reduced fertility, and under primitive conditions it is very likely that they conferred a biological disadvantage on the individual. The fact that they are so common suggests that during the course of evolution they have also conferred some compensatory advantage. Various suggestions about this advantage have been made, and two are reviewed with particular reference to their heuristic value.

7. The hibernation model leads us to consider depressive states as ways of avoiding seasonal variations to which we are ill adapted. It turns our minds to the possible nature of these variations and to the stimuli which might have signalled their advent. It is possible that knowledge of the neuroendocrine mechanisms of hibernation might be relevant to depression.

8. The dominance hierarchy model is based on the social system of baboons and macaques. Changes in dominance status are times of instability for the social group, and it is suggested that depressive behaviour on the part of the animal descending the hierarchy enables the change to be made more smoothly. The model indicates the need for further observations of these events in the field and the laboratory, and for study of similar factors in the case of patients who exhibit depressive behaviour.



## Appendix

Brief case histories of monozygotic twins reared apart, one or both of whom has suffered from an affective disorder.

1. Rosanoff *et al.* (59). Case 1. Male, born 1909. Mother hospitalized with involutional melancholia, younger brother with hebephrenic schizophrenia. Separated when a few months old, John remaining with parents, William going to live with uncle 200 miles away. They have seen each other only rarely, and that only in recent years. Both have pyknic build.

"John was the first to develop psychotic symptoms, although William was the first to be hospitalized. John had to leave school at the age of 13 years and go to work in a mill, as his father died and he had to help support his mother and sisters. He has been somewhat unstable and never seems to have held any one position very long. Lately he has worried considerably over the family finances. His psychosis developed gradually in the early part of 1930, i.e., at the age of 21 years. He developed fanciful ideas of a semi-religious nature, said that Arnprior (the town in Ontario where he lived) had a connection with Noah's ark, gave up his job to spend his time hunting for the landing place of the ark, also for the exact site of the garden of Eden which, too, he said, was in that vicinity. He became very excited over this, and irritable and assaultive when contradicted. By this time (May, 1930) his twin brother suddenly developed a mental breakdown and was committed. When John heard of this he became even more upset. He went down the street and assaulted several people, who, he said, sneered at him about this, although they had not even spoken to him. He was arrested for assault and battery and held for a month in the Arnprior jail, from where he was committed to the Ontario Hospital at Kingston on July 31, 1930.

"Upon admission he was very unstable emotionally, quarrelsome, and assaultive; extremely untidy, smeared himself and the walls; showed distractibility with marked tendency toward sound associations. In a short time, however, he quieted down, developed full insight, laughed at his former religious ideas, and was anxious to go to work again. He was discharged as recovered on January 29, 1931. At the time of our observation of the case, which was in the middle of August, 1932, he was in good health and well adjusted at home and at his work.

"William had always been very jolly, fond of company, 'the life of the party'. As has already been stated, unlike John, he was raised in comparative comfort. His psychosis developed suddenly and under quite different circumstances. In the spring of 1930 he applied for a position on the railroad, but did not get it. He became quarrelsome and assaultive; went out and placed obstructions on the railroad track of the line that would not hire him; then developed the idea that they were going to hang him for it. He was arrested on a technical charge of vagrancy and promptly committed to the Ontario Hospital at Kingston on May 10, 1930.

"Upon admission he was found to be very unstable and variable emotionally, showed distractibility, was quarrelsome and assaultive. He, too, cleared up in a short time and was discharged as recovered on January 29, 1931. At the time of our observation of the case, which was in August, 1932, he was at home, in good health, and getting along quite satisfactorily."

*Comment:* The length of follow-up is short, and it may be that the final diagnosis would have been schizophrenia rather than manic-depressive psychosis.

2. Stenstedt (69). Case 106. Female, born 1892. Separated age 1 and very little contact since then. Both raised in poor circumstances.

Proband brought up by parents until age 10 when she started resident domestic work. Married age 22, had 5 children, went out to work because of poverty. Age 32 husband died. Married again, pregnant, at age 47. Husband fell ill and so had to work again. About 10 months after birth of child became nervous, sleepless, with headaches and hypochondriacal ideas. Over the next 6 months, became more depressed and was admitted to the asylum, where depressive and hypomanic phases alternated. Social recovery, but still has depressive episodes 10 years later.

Cotwin lived with aunt until her marriage at age 25, when she saw a doctor several times because she was nervous and "imagined dreadful things". Afraid of contracting Tb, found everything against her, difficult and dreary; felt restless. Unable to work for about half a year. Depressed and unco-operative when seen by Stenstedt.

*Comment:* The illnesses are similar in many ways, although there is a large difference in age of onset and only one was hospitalized. We do not know whether the cotwin also had hypomanic phases.

3. Shields (63). Case Sf3. Female, age 30. Separated at 13 months, lived in nearby towns and frequently saw each other. Both described well-marked symptoms of anxiety and depression lasting 2 or 3 months, one after mother's death, the other in relation to difficulty in conceiving. Probably neither had medical treatment.

4. Shields (63). Case Sf5. Female, age 32. Separated at birth, they see each other rarely. Only one has had an experience which she described as a minor nervous breakdown occurring after the death of her child aged 7 weeks. She was in a state of indecision about whether to have another child, could not get the thought of babies out of her mind, and got so worked up that she and her husband decided it would be better to sleep apart. No medical treatment for this illness, which may have been a mild affective disorder. The other has remained well in spite of five miscarriages (after which she gave birth to MZ twin daughters).

5. Shields (63). Case Sf11. Female, age 38. Separated age 8 when Molly went to live with a strict and demanding grandmother. Molly had fits of depression age 12; during the war she "went to pieces" and could not stay on her own, she was treated for neurasthenia and improved when her husband was taken off night work. Dorothy had a hysterectomy age 32, since when she has been liable to "sudden unexplained periods of depression (untreated), lasting 1 or 2 weeks, in which she is weepy and her sleep is affected".

6. Shields (63). Case Sf14. Female, age 40. Separated age 3 months; went to same school but had little contact. Edith brought up by mother who was highly strung and inconsistent. Edith was always the more neurotic twin, and had two nervous breakdowns age 22 and 25 in one of which she saw a psychiatrist, diagnosis depression. Unlike Edith, Millicent remained single, and had more physical illness, including liver disease secondary to mitral stenosis; but she had no mental disorder of any sort.

7. Shields (63). Case Sf19. Female, age 43. Father a Scandinavian ship's carpenter, several hospital admissions with manic and depressive attacks. Separated age 4, when the father sold Berta to a Latin American doctor in order to pay his debts. Herta was brought up in poor circumstances in Scandinavia, but came to run her own restaurant; she has had several attacks of depression, in one of which she attempted suicide, in another was hospitalized with a diagnosis of commotio cerebri seq. neurosis. Berta was brought up in comfortable circumstances; she has consulted "many fine specialists" for attacks in which she feels sad and nervous, can't sleep, loses her appetite, and has many somatic complaints. Her letters to Herta reveal marked swings of mood. She has not been hospitalized or seen a psychiatrist, as far as is known.

8. Shields (63). Case Sf21. Female, age 47. Separated from birth to the age of 12, since when they have been close. Nine months ago Nancy had an operation for carcinoma of the breast followed by radiotherapy. During this time Mary was very upset, lost 1½ stone, cried all the time, thought the end of the world was coming, could not sleep without sedatives; no psychiatric treatment. Nancy herself during this time has only suffered some tiredness and difficulty in sleeping.

9. Shields (63). Case Sf26. Female, age 55. Separated at 6 months, meet occasionally since age 17. Both are of anxious disposition, both had breakdowns in middle life in which they "cried all the time", were advised to go into hospital by their doctors and both refused.

10. Juel-Nielsen (29). Case 4. Female, age 46. Separated only from age 1 to 7. Ingegard has had at least seven admissions to hospital for depression since age 39, diagnosed neurotic depression, psychogenic psychosis and manic-depressive psychosis (depression). On the last occasion she made a rapid and good response to 6 ECT. Monika has had 42 admissions to hospital, mainly for gynaecological troubles, but one for attempted suicide. She had previously attempted suicide age 28. No formal psychiatric diagnosis was made, but at her 24th admission age 34 she complained of bad nerves and reduced libido in addition to somatic complaints, and she became a proband in a psychiatric investigation; it was then thought that because Ingegard had not manifested nervous symptoms, genetic factors were unlikely to be important in Monika's case.

11. Juel-Nielsen (29). Case 6. Female, age 49. Separated age 3, but brought up in the same town. Marie had recurrent bouts of nervous symptoms from age 30, for which she was admitted at least once to a general hospital, complaining of nervousness, insomnia, loss of weight, fatigue, difficulty in concentration, giddiness, pressure in the chest and back; she was observed to be depressed; diagnosis neurosis (neurasthenia). Martha has never been in hospital; she has migraine, like her twin, and in recent years her headache has become almost constant; she regularly takes a sleeping pill for insomnia. Martha became a farmer's wife at 32 and had 6 children, whereas Marie never married. Otherwise there are no obvious environmental differences to explain the difference in psychiatric history.

12. Juel-Nielsen (29). Case 8. Female, age 54. Separated at three weeks, occasional contact since age 20. Hanne married at 22, had two children, and was widowed at 36. She was admitted at 38 with nervous symptoms, thought to be thyrotoxic; again at 52 with loss of weight and had nerves, among other symptoms; 8 months later with eczema of the palms, and a psychiatrist reported that she had disturbances all over the body, lack of energy, depression and restlessness, and he noted she was absorbed in her symptoms, diagnosis depressive neurosis.

Signe married a widower at 47. She had admissions at 39, 45 and 54 for anxiety, depression and multiple somatic complaints, including pains all over the body. On the last occasion she was referred to the psychiatric clinic and given 8 ECT with some improvement. Diagnosis depressive neurosis.

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