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The Relationship between Genetic and Precipitating Factors in Depressive Illness

By JOHN POLLITT

Introduction

Scientific studies of the families of depressed patients have shown that the risk of development of similar illnesses for close relatives is greater when the illness of the index case began relatively early in life than when it began later. These studies have included both manic-depressive and single episode endogeneous depressions, and no account has been taken of the mode of precipitation of the illnesses. It has been postulated that (a) the penetrance of the gene may be lower in those families with late onset of depression, and (b) that depressive illness may be of diverse aetiology, so that genetically determined forms appear earlier in life and those which are not genetically determined occur later (Hopkinson and Ley 1969).

To clarify the relationship between aetiology of depression and genetic factors in a homogeneous sample the present prospective study was made.

Method

Patients seen consecutively suffering from endogenous or typical physiological depression appearing as a solitary episode were examined, the clinical and aetiological factors being explored first.

The family history was then taken and later verified by reference to the relative affected or to another relative and the physician who had treated the relative affected. Those with a history of cyclical depression, manic or hypomanic episodes and those who had had more than one previous attack or an episode less than four years previously were excluded. It was also necessary to reject 25 patients for the following reasons:

1. Both physical and psychological stress preceded the illness.

2. Subsequent observation showed that the depressive illness was followed by cyclical depression or hypomanic episodes.

3. The family history could not be confirmed.

The remaining 142 patients, 26 or whom had had one previous episode more than four years before the present illness, were divided into main groups according to the apparent aetiology of the depressive illness. The first group consisted of those cases in which a physical or physiological disturbance preceded the development of first symptoms by not more than eight weeks, and in which no relevant psychological factors could be determined. These patients labelled Group A, included 24 males and 43 females, the mean age being 36 years. The second group contained those patients who did not experience a physical or physiological disturbance before the onset of the illness, and was called Group B. In this group 39 males and 36 females were included and the mean age was 38 years.

Patients in Group 'A' were placed in subcategories according to the type of physical stress preceding the onset of the depressive illness. The grouping and criteria were as follows:

Group I

(Twenty-four patients.) Those whose illness followed a severe virus or bacterial infection.

Group II

(Eighteen patients.) Those whose illness followed childbirth or endocrine disturbance. This group was composed only of females.

Group III

(Twenty-five patients.) Miscellaneous physical or physiological stress, including weight loss due to restrictive dieting, gross over-work, drugs or surgical operation.

Patients in Group 'B' were sub-divided into three groups according to the following criteria:

Group I

(Fourteen patients.) Those in whom a severe psychological stress occurred within eight weeks of the onset of the illness. These patients had experienced no stress of similar severity previously, or, if they had, no abnormal psychological sequelae developed after that stress.

The nature and severity of stress was such that the development of depression was a possible predictable outcome in the patient concerned.

Group II

(Forty-two patients.) Although the patient believed that his illness was precipitated by psychological stress, the circumstances were such that from the medical point of view this could be regarded only as a possibility.

Group III

(Nineteen patients.) No detectable preceding stress. The patient was unaware of psychological stress before the onset of the illness and there was no reason to believe that his or her view was inaccurate.

The morbidity risk among relatives for each main and sub-category was calculated by Weinberg's short method, the period of manifestation 20 to 70 years of age being used. As the numbers were small, parents and siblings were taken together.

For secondary cases, parents and siblings only were considered. Criteria similar to those used for the probands illnesses were employed, but cyclical depressions and manic depressive illnesses were included. A total of 49 cases were confirmed, the majority having been under the care of consultant psychiatrists whose records were made available. In five cases the notes of general practitioners were used, and seven affected relatives were interviewed personally. Among the whole group of siblings were 3 maternal half-siblings (1 male, 2 female), and 6 paternal half-siblings (5 male, 1 female). These were counted as $\frac{1}{2}$ in calculating the bezugziffern.

Results

Morbidity risks for Group 'A' and 'B' and their sub-categories, the data from which they were calculated and the mean age of each group are shown in Table I.

The morbidity risk for the whole group is $14{\cdot}8 \pm 1{\cdot}9$ per cent, which is within the range given by Stenstedt (1952) for parents, siblings and children of manic-depressives. However, this is derived from a much lower figure from Group 'A' (physical series) 9·4 per cent and a much higher figure for Group 'B', 19·2 per cent (non-physically precipitated). The actual differ-

TABLE I

Distribution of parents and siblings, and morbidity risks for male and female probands in Groups 'A' and 'B' and their subcategories

Category	N	Mean age of probands (years)	Age at disappearance from observation 0–19	20–70	70–	Bz	Number affected	Morbidity risk (%)	S.E.
Group 'A'									
I	24	35	10	86·5	13	56·5	4	7·1	3·4
II	18	32	4	64·0	3	35·0	7	20·0	6·8
III	25	40	8	95·0	21	68·5	4	5·8	2·8
Total	67	36	22	245·5	37	160·0	15	9·4	2·3
Group 'B'									
I	14	39	3	67·0	9	42·5	5	11·8	4·9
II	42	38	13	159·0	23	102·5	22	21·5	4·1
III	19	36	5	79·5	8	47·75	10	20·9	5·9
Total	75	38	21	305·5	40	192·75	37	19·2	2·8
Grand total ..	142	37	43	551·0	77	352·5	52	14·8	1·9

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ence of 9·9 per cent is well over twice the S.E. of the difference 3·7 per cent, and therefore significant. Comparison of the two purest subcategories of Group 'A' I (virus and bacterial infections) and Group 'B' II (probably psychological) shows a significant difference also (14·4 per cent; S.E. of Diff. 5·3), despite much smaller numbers. It is noteworthy that the risk in puerperal and endocrine cases ('A' II) is high (20 per cent) and is similar to the risk for non-physically precipitated cases in Group 'B'. The difference between the morbidity risk of Group 'A' II and Group 'A' I and III combined is not significant.

Kay (1959) and Hopkinson (1964) found a higher morbidity risk among relatives of patients whose illnesses were of later onset in life than in relatives of patients whose illnesses developed earlier. To determine whether this phenomenon had been excluded by the separation into aetiological categories, the morbidity risks for relatives of patients below 35 years of age and for those 36 or more years of age were calculated for Groups 'A' and 'B'. Table II shows the results, indicating that the overall lower morbidity risk in Group 'A' and the higher risk in Group 'B' are each made up of lower risks for the patients over 35 and higher risks for those 35 and below. The difference between the two age groups is statistically significant in each case (Group 'A' observed difference 10·4, S.E. 4·4, Group 'B' observed difference 17·2, S.E. 6·6).

Discussion

Hopkinson and Ley (1969) found a sudden decrease in the morbidity risk for depressive illness among relatives of patients suffering from depression after the age of 40 in a series which included cases of manic-depressive disorder and endogenous depression. The explanation put forward was that early onset cases may represent genetically determined illnesses likely to recur, later onset cases being 'symptomatic' in type.

In the present study, cases of the manic-depressive variety were excluded as far as possible on clinical grounds, but a significant difference in morbidity risk for parents and siblings was still evident between those with early onset and those with a later onset of illness. Separation of cases into those in which a physical factor was considered responsible for precipitation of the illness and those in which a psychological factor was responsible shows a significantly higher morbidity risk for relatives of the latter.

These findings may be interpreted by using the concept of a threshold for precipitation of 'solitary' depressive reactions; the threshold level, initially determined by genetic factors, being influenced later by upbringing and maturation.

The vulnerability of an individual to a depressive reaction of endogenous or physiological type would then depend on:

1. Genetic factors.

Table II

Morbidity risks of patients in Groups 'A' and 'B', above and below the age of 35

Category	N	Age at disappearance from observation 0–19	20–70	70–	Bz	Number affected	Morbidity risk (%)	S.E.
Group 'A'								
35 and below ..	36	21	135	6	73·5	11	15·0	4·2
36 and above ..	31	1	110·5	31	86·5	4	4·6	2·3
Total	67	22	245·5	37	160	15	9·4	2·3
Group 'B'								
35 and below ..	33	18	121	1	61·5	19	30·9	5·9
36 and above ..	42	3	184·5	39	131·25	18	13·7	3·0
Total	75	21	305·5	40	192·75	37	19·2	2·8

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2. Modification of the level of threshold by upbringing.

3. Modification of threshold by age.

4. Vulnerability of nervous system to physical stress.

5. Personality, representing vulnerability to psychological stress and capacity to avoid or deal with this.

In a mixed population the expected finding would be for those with high morbidity risks among relatives to succumb to depression earlier and those with low risk to fall ill in later life. However, the effects of age and increasingly obsessional behaviour could account for the greater incidence of depression in mid-life and later by a mechanism of increasing hypothalamic 'suppression', as suggested earlier (1965), despite the lower morbidity risks found.

The present findings suggest that the nature of stress may also be important. Patients who succumbed to an apparent physical or physiological stress had relatively high thresholds whereas in those who became ill after psychological stress it was low. In a population of homogeneous cultural background this finding is in keeping with the theoretical framework outlined. Assuming that both physical and psychological stresses are met with by everybody, the effect of these stresses would depend on the individual's capacity to monitor and avoid or resolve them. Clinical evidence suggests that the types of physical stress encountered were not monitored consciously and could not be offset, whereas the psychological stresses, by definition, were well recognized by the sufferers. If the present findings are substantiated, it can be postulated that a low genetic influence is necessary in the case of physically precipitated depression, for the stress is unmodified; whereas, since psychological stress can be reduced by defence mechanisms and human help, a much greater genetic influence must be present to lower the threshold sufficiently for this type of stress alone to pass it.

One criticism of the study is that the assessment of aetiology of the depressive illness and the subsequent classification of patients may have been influenced by the author's awareness of the family history and possible genetic factors at the initial interview. However, patients were classified long before the family history was confirmed by documentary evidence, and the findings of an exceptionally high morbidity risk among those with supposed puerperal and endocrine precipitants, whose illnesses were initially regarded as undoubtedly of physical origin, is against this view.

If these findings can be substantiated, the aetiological analysis of illnesses of depressive probands becomes most important. Stenstedt (1952) has shown that there is a marked difference in morbidity risk between manic-depressive illness and involutional melancholia; Kay (1959), Hopkinson (1964) and Hopkinson and Ley (1969) demonstrated that the age of onset of the proband's depressive illness also influences the morbidity risk profoundly. It is suggested from the present study that the proportions of probands' illnesses precipitated by 'physical' or 'psychological' factors may influence markedly the results of genetic study.

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