Abnormality on Paternal and Maternal Sides: Observations in Schizophrenia and Manic-depression

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In a previous communication (Slater, 1966) a computational model was offered which might provide guidance about the expected distribution of secondary cases on the paternal and maternal sides of a family, starting from an index case suffering from a condition whose genetical basis was polygenic. Supposing that two such secondary cases were found, in what proportion of instances could one expect both to be on the one side of the family, paternal or maternal, i.e. unilaterally distributed, and in what proportion could one expect one case to be on the paternal side and the other case on the maternal side, i.e. a bilateral distribution? With a very rare condition of single-gene dominant type, one would expect all affected relatives in the ascendance of an index case to be unilaterally distributed, either all paternal or all maternal. This suggests that observation of secondary cases in a condition whose genetic basis was unknown might provide useful information to help one to decide whether polygenic inheritance was a sufficient explanation or whether dominance was to be taken into account. The expectations resulting from dominance, however, get less clear if the condition is a common one, and still more so if there is diminished penetrance. To see, for comparison, what might result from polygenic inheritance, computations were carried out on the basis of a number of simplifying hypotheses. They led to the somewhat rough and ready estimate that, in the case of second-degree relatives (grandparents, uncles, and aunts), pairs of affected relatives should be approximately twice as often unilaterally as bilaterally distributed. The empirical figure of 22:10 would be shifted to the benefit of bilateral pairs with the taking into account of relatives of remoter than second degree (to the other side if first-degree relatives, i.e. parents, entered

largely into the picture). The estimate also took no account of the fact that in any family the numbers of relatives investigated would be limited; allowance for this limitation would also lead to the expectation of a larger proportion of bilateral pairs.

What now follows is the account of an attempt to turn the model described above to practical account. Both with schizophrenia and manic-depressive illness evidence has accumulated to show that genetical factors are involved. In both conditions the observational data could be accounted for either by a single major gene manifesting with diminished penetrance in the heterozygote, or by a polygenically determined predisposition manifesting in a qualitative change to clinical abnormality if it once exceeded a given margin of tolerance. The application of the model might help us to prefer one or other of these alternative hypotheses.

We have examined all the in-patient case records of the joint Bethlem Royal and Maudsley Hospitals for the two years 1961 and 1962, taking out for study all those receiving a diagnostic code number (International Classification of Diseases) of 300 (schizophrenic disorders) or 301 (manic-depressive reaction). Where the clinical record showed a family history positive in our sense, the notes were examined very completely for any further family information. We have to thank Miss Vera G. Seal for a second check on this part of the work. The family was included in our statistics if two or more relatives in the ascendance of the index patient were thought to have a psychiatric abnormality akin to that of the patient. The relatives coming in question were parents, uncles and aunts, grandparents, sibs of a grandparent, and cousins. All such relatives were accepted for inclusion who were recorded as having suffered from psychosis, or 'nervous breakdown', or had committed suicide, or had been admitted to a mental hospital for any

TABLE I
SCHIZOPHRENIA

Case No.	Relatives								Total		Combinations		
	Paternal				Maternal				Pat.	Mat.	Pat.-Pat.	Pat.-Mat.	Mat.-Mat.
	1	2a	2b	3	1	2a	2b	3					
N 1650	—	—	—	—	1	1	1	1	—	4	—	—	6
N 2136	—	—	1	—	—	—	2	—	1	2	—	2	1
M 2412	1	—	1	—	—	—	—	—	2	—	1	—	—
N 9042	1	—	2	—	—	—	—	—	3	—	3	—	—
N 0292	—	—	—	2	1	1	—	2	2	4	1	8	6
K 1977	—	—	2	—	—	—	—	—	2	—	1	—	—
N 1444	—	—	—	—	—	1	2	—	—	3	—	—	3
F 9271	1	1	—	2	—	—	—	—	4	—	6	—	—
K 0941	—	—	—	—	—	2	—	—	—	2	—	—	1
N 8202	1	—	—	—	1	1	—	—	1	2	—	2	1
M 0275	—	—	—	—	1	1	—	—	—	2	—	—	1
P 1052	—	—	—	—	1	1	—	—	—	2	—	—	1
P 0409	—	1	1	—	—	—	—	—	2	—	1	—	—
P 0032	1	—	1	—	—	—	—	—	2	—	1	—	—
P 0049	—	—	1	—	—	1	—	—	1	1	—	1	—
P 0181	1	—	1	—	—	—	—	—	2	—	—	—	—
F 1238	—	—	—	3	—	—	—	—	3	—	3	—	—
J 1636	1	—	—	—	—	—	1	—	1	1	—	1	—
H 1577	1	—	—	3	—	—	—	—	4	—	6	—	—
Total	8	2	9	11	3	4	11	5	30	23	24	14	20

condition other than those specifically excluded. Conditions which were not regarded as a qualification for entry into the statistics included epilepsy, organic states, mental deficiency, alcoholism, senility, dementia, delirium, 'nerves', neurosis, personality disorder, and attempted suicide. The distribution of the secondary cases fulfilling these conditions, which we found in the families of the index patients, are as shown in Table I and Table II.

Parents are shown under column 1, parent's parents under 2a, parent's sibs under 2b, and cousins under 3.

Combinations of affected relatives in each of these families can be counted in terms of pairs, $n(n-1)/2$ being the possible number of combinations in pairs of n affected relatives. It will be seen that in the families of schizophrenics we had 14 bilateral pairs out of 58, instead of an expected 19.3, and in the

TABLE II
MANIC-DEPRESSION

Case No.	Relatives								Total		Combination		
	Paternal				Maternal				Pat.	Mat.	Pat.-Pat.	Pat.-Mat.	Mat.-Mat.
	1	2a	2b	3	1	2a	2b	3					
N 1514	—	—	1	1	—	—	—	—	2	—	1	—	—
M 0868	—	—	—	—	—	—	2	3	—	5	—	—	10
M 2425	—	—	—	—	1	—	1	—	—	2	—	—	1
N 0271	1	1	—	3	—	—	—	—	5	—	10	—	—
M 1928	1	—	2	—	1	—	1	—	3	2	3	6	1
N 1562	—	—	—	1	—	—	1	—	1	1	—	1	—
M 2089	1	1	2	1	—	—	—	—	5	—	10	—	—
N 0161	—	1	1	1	—	—	—	—	3	—	3	—	—
N 0157	—	1	—	—	—	—	1	—	1	1	—	1	—
N 0867	1	—	1	—	1	—	1	—	2	2	1	4	1
L 1301	—	—	1	—	1	—	1	—	1	2	—	2	1
L 0248	—	—	—	—	1	—	1	—	—	2	—	—	1
M 1881	—	—	—	—	1	—	1	—	—	2	—	—	1
N 1084	1	1	2	1	—	—	1	—	5	1	10	5	—
P 9065	1	—	1	1	—	—	—	—	3	—	3	—	—
N 1962	—	—	—	—	—	2	3	—	—	5	—	—	10
P 0332	—	—	—	—	1	1	—	—	—	2	—	—	1
B 4897	—	—	—	—	1	1	1	—	—	3	—	—	3
P 9008	1	—	—	—	1	—	1	—	1	2	—	2	1
N 1020	—	—	—	—	1	1	—	—	—	2	—	—	1
P 1296	—	—	1	1	1	—	—	—	2	1	1	2	—
P 0786	1	—	—	—	1	—	—	—	1	1	—	1	—
K 2086	—	—	—	—	—	2	—	—	—	2	—	—	1
M 1858	—	—	—	1	—	—	1	—	1	1	—	1	—
Total	8	5	12	11	12	3	14	10	36	39	42	25	33

families of the manic-depressives 25 bilateral pairs instead of an expected 33·3. In each case there is a deviation in the direction to be expected if dominance played a role. However, the assessment of statistical significance requires more consideration.

If we were to accept the distribution of pairs as they stand, without correction, we should be giving excess weight to the families with four or more affected individuals, and giving an insufficient weight to the families with only two affected. Our information consists in independently observed individuals, and each family should have a weight simply proportionate to this number. To make an adequate correction, all that is required is to multiply findings in these families by $2/(n-1)$, while retaining the proportionate distribution between the three different kinds of combination. Thus the family of the manic-depressive patient M 1928 can be counted as giving us observations of, respectively, 1·5, 3·0, and 0·5, total 5 (instead of $3+6+1=10$). When all these values are summed we have a total of 53 in the schizophrenic group, and 75 in the manic-depressive group, as we should have. The results of this summation are shown in Table III.

TABLE III

	Observation	Expectation
Schizophrenic families		
Unilateral pairs	41·8	35·3
Bilateral pairs	11·2	17·6
Total	53·0	53·0
Manic-depressive families		
Unilateral pairs	53·3	50·0
Bilateral pairs	21·6	25·0
Total	75·0	75·0

The values of χ^2 calculated from the figures of Table III are for schizophrenia 3·55 and for manic-depression 0·67. Rather surprisingly, the evidence for dominance is stronger in schizophrenia than in manic-depression. A somewhat sterner test might be made by eliminating any consideration of first-degree relatives, since in the computational model they shift the balance relatively more in the unilateral direction. If we do this we find 30 unilateral and 7 bilateral schizophrenic pairs (with weighting as previously described), and 35 unilateral and 14 bilateral manic-depressive pairs. Here χ^2 is 3·46 for the schizophrenic distribution, and 0·50 for the manic-depressive one. The manic-depressive figures are clearly compatible with a polygenic genetical basis. Applying a one-tail test to either of the values of χ^2 in the schizophrenic families, the value of p is less than 0·05; and we conclude that the findings support the hypothesis that there is an element of dominance in the genetical predisposition to schizophrenia.

Summary

The clinical records of patients admitted to the in-patient departments of the Bethlem Royal and Maudsley Hospitals for the two years 1961 and 1962 were searched for cases with evidence of other family members similarly affected on either the paternal or maternal side, or on both. The distribution of such cases, either unilateral or bilateral, was compared with expectations based on a previously published computational model. It was concluded that in the schizophrenic families the distribution tended to support a hypothesis involving dominance, but not in the manic-depressive families.

REFERENCE

- Slater, E. (1966). Expectation of abnormality on paternal and maternal sides: a computational model. *J. med. Genet.*, 3, 159.