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Some Recent Developments in Psychiatric Genetics*

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Summary. The methods and results of some recent family, twin and adoption studies of childhood behaviour disorders, crime, alcoholism, psychopathic personality and neurosis are briefly described. The data of Slater (1938) on the parents and children of manic-depressives are reanalysed. Bipolar affective illnesses were more frequent in the families of bipolar than unipolar probands. There was no support for sex-linked inheritance in either group or for further genetic subdivision of the unipolar group according to age of onset or alcoholic or psychopathic family history. It is suggested that for the time being we may have to be satisfied with three broad and aetiologically overlapping clinical types of depression: bipolar, unipolar and reactive.

Key words: Genetics — Twins — Adoptions — Behaviour Disorder — Affective Disorder, Unipolar and Bipolar.

It is a great honour and privilege to be able to speak to you today as a member of the famous faculty of medicine of Zürich University where schizophrenia if not born was certainly baptized.

The last time I was invited to speak at the Burghölzli it was on concepts of heredity for schizophrenia (Shields, 1971); and since then my colleague, Dr. Gottesman, has spoken to you about the study we carried out together on schizophrenic twins from the Maudsley Hospital (Gottesman and Shields, 1972). There have been interesting and problematic developments in genetic schizophrenia research since then, notably further reports on Danish adoptees and their families by Rosenthal, Kety and their colleagues (Kety, 1974; Wender *et al.*, 1974; papers in Mednick *et al.*, 1974). However, I have decided to speak about something different as a change. I do not wish to talk about manic-depressive psychosis either—or at least not exclusively. It would be much more appropriate for me to listen to a lecture from Prof. Angst on endogenous depressive psychoses than for you to listen to such a lecture from me. Though I intend to present some further data on the inheritance of unipolar and bipolar psychoses, I would prefer to do so in the course of a general presentation of some recent developments in behaviour and psychiatric genetics which I believe are of interest and which may be new to you. I shall first illustrate the application of twin studies and adoption studies to the behaviour disorders of childhood and to the socially defined behaviour of crime. Then, after brief mention of recent work on psychopathic personality, alcoholism and neurosis, I shall conclude by re-analysing some of the data on manic-depressive psychosis which Slater (1938) collected in Munich before the war. I shall do so in the light of recent views about unipolar and bipolar psychosis and sex-linked inheritance.

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Genetic influences on childhood development, on neurosis and on crime are likely to be polygenic: inheritance will be complex; the behaviour by which the disorder is recognised will be far removed from the primary molecular or biochemical effects of single genes; more than one gene will be involved, and so will many environmental factors; and the particular combination of multiple causes will vary from case to case.

Childhood Behaviour Disorder

One of the criteria of polygenic inheritance which have been suggested by Carter (1969) relates to disorders in which the sex ratio deviates markedly from unity. Patients of the less frequently affected sex will be more extreme deviants than those of the more frequently affected sex. Hence the risk to their relatives will be correspondingly higher. This has been shown by Carter and Evans (1969) to be true for congenital abnormalities like pyloric stenosis. An early example of a behaviour disorder in childhood in which the same principle holds is stuttering. Boys are more than twice as often affected as girls. A study carried out in Newcastle by Kay (1964) showed that parents and sibs of female stutterers tended to be more often affected than those of males (Table 1). The theory is that girls require more of the predisposing genes than boys if they are to become stutterers; hence their parents and siblings should have more of the genes and therefore include more stutterers. Kay also found that the risk was higher in the families of the more severe clinic cases than in cases obtained from a survey in the schools. This relation between severity and morbid risk is another criterion of polygenic inheritance. Similar effects of sex and severity occur in studies of crime, as I shall show later.

But first I should like to present some further recent data on childhood behaviour disorders in twins. In New York Bakwin (1970, 1971a, b, c and d, 1973; Bakwin and Davidson, 1971) studied several such conditions in a large sample of middle-class twins. There were usually 338 same-sex pairs, 204 of them monozygotic. They were not selected on account of abnormality. Though they were not a random cross-section of the entire twin population of New York, they however can be used to illustrate an interesting application of the twin method to population data. In Table 2 I have reanalysed Bakwin's data to show the relationship between concordance and prevalence—that is, between the observed and the expected rates in MZ and DZ twins of affected cases. For most disorders prev-

Table 1. Stuttering according to sex of proband and relative (after Kay, 1964)

	Stutterers (percent and standard error)	Ratio to risk in same sex in general population
Female relatives of 175 male probands	6.3 ± 1.4	3.2
Male relatives of 175 male probands	18.2 ± 2.2	4.6
Female relatives of 38 female probands	12.9 ± 4.3	6.5
Male relatives of 38 female probands	27.5 ± 5.7	6.9

Table 2. Behaviour deviations in a large sample of twins (Source: Bakwin, 1970, 1971a, b, c, and d; Bakwin and Davidson, 1971)

		Incidence[a]		Concordance		Excess incidence in co-twins	Sig. level of MZ:DZ difference
		Cases	Percent of all twins	Co-twin also affected	Percent of all cases		
Reading disability	MZ	57	14.0	52	91.2	×6.5	< 0.001
	DZ	40	14.9	18	45.0	×3.1	
Enuresis	MZ	89	21.7	72	80.9	×3.7	< 0.01
	DZ	57	21.4	30	52.6	×2.5	
Constipation	MZ	39	9.5	32	82.3	×8.7	< 0.005
	DZ	20	7.4	6	30.0	×4.1	
Sleepwalking	MZ	28	7.1	18	64.3	×9.1	< 0.04
	DZ	15	6.0	2	13.3	×2.2	
Car sickness	MZ	80	20.2	68	85.0	×4.2	< 0.001
	DZ	45	19.2	20	44.4	×2.3	
Nailbiting	MZ	128	31.4	102	79.7	×2.2	< 0.001
	DZ	78	28.0	38	50.7	×1.8	
Fingersucking	MZ	126	30.9	94	74.6	×2.4	Non-sig.
	DZ	63	23.6	38	60.3	×2.6	

[a] The totals on which the incidences are based range from 396—408 MZ and 236—268 DZ twins (individuals).

alence was similar in both kinds of twin. For example, reading disability, as assessed by Bakwin, occurred in 14% of individuals from MZ pairs in his sample and in 14.9% of DZ twins. MZ twins as such are at no greater risk for behaviour disorder than DZ twins. However, the twin partner of a backward reader was also backward in 52 of the 57 MZ cases (that is, a proband method concordance rate of 91%), compared with 18 of 40 DZ cases (45%). The MZ co-twin rate was 6.5 times the prevalence in Bakwin's total sample, the DZ rate 3.1 times.

Findings were somewhat similar for enuresis, constipation, sleepwalking, car-sickness and nail-biting, suggesting that genetic factors contribute to the aetiology. Of the conditions studied, only fingersucking failed to show an MZ:DZ difference. In several of these conditions, the rate for sibs and co-twins was higher when a parent had been similarly affected in childhood than when a parent had not been affected, thus satisfying another of Carter's criteria for polygenic inheritance. There was, however, no indication that the risk was higher for the relatives of females in the case of enuresis or reading disability which are disorders which occur more frequently in boys than girls. A possible reason for this in the case of reading disability is that a major dominant gene may play an important part in a proportion of cases of dyslexia (Hallgren, 1950).

There was usually no tendency for the various disorders to be related in Bakwin's study—the car-sick were not enuretic, for instance. This tends to confirm our earlier work from the Maudsley that genetic factors influence the nature of a disorder when it occurs rather more than they influence its presence or severity (Shields, 1954; Shields, in press). A word of caution is required about generalizing about the extent of genetic influences in behaviour disorders from Bakwin's

sample. Associations with family size and social class, and differences in prevalence according to time and place, point to the influence of environmental factors (Rutter, 1973; Rutter *et al.*, 1970). Bakwin's sample varied little in these respects.

Criminal Behaviour

Juvenile delinquency is one condition in which the evidence of three twin studies (see Shields, in press) suggests that the genes make little or no difference. If one of twin boys gets into trouble with the police, the other is quite likely to do so too and it makes little difference whether they are genetically identical or not. In other words, concordance was high in both MZ and DZ pairs. However, the earlier twin studies of crime in adults suggested that genetic influences played a considerable, if indirect, part in the persistent psychopathic criminal. Since such offenders often begin early, juvenile delinquents—and probably adult criminals as well—may be a heterogeneous group.

Nevertheless, when one simply looks at criminal offences of any kind—crimes committed doubtless for a variety of reasons—there is evidence that genetic influences are among those that contribute to crime as a whole. This evidence comes from studies of twins and of adoptees and their families, based on complete Danish population registers.

Twin Studies

Christiansen (1970, 1974) studied the criminal records of all Danish twins born between 1870 and 1920. We may examine his findings in male and female MZ and same-sexed DZ pairs in the same way as we did those of Bakwin, comparing the population prevalence and the concordance for crime among co-twins. From Table 3 you will see that there were 650 male twins from MZ pairs. 14.8% had a criminal record. This was a little higher than the corresponding rate of 11% among DZ males. (One might speculate about whether this might be because the MZ partner of a known criminal is more likely to be accused and convicted than the DZ partner.) Of the 96 male MZ criminals, 50 or 52% had a criminal co-twin. This observed rate is 3.5 times the prevalence or expected rate of 14.8% in male MZs. Dizygotic male concordance for crime was 22% or twice the expected rate

Table 3. Twins and criminality in Denmark (data of Christiansen, 1974)

	All same sex twins			
	MZ		DZ	
	Males	Females	Males	Females
Pairs	325	328	611	593
Individuals	650	656	1222	1186
Criminals	96	17	135	29
Prevalence	14.8%	2.6%	11.0%	2.4%
Criminals with criminal co-twins	50	6	30	4
Concordance (proband method)	52.1%	35.3%	22.2%	13.8%
Concordance: prevalence ratio (O/E)	3.5	13.6	2.0	5.6

of 11%. Thus there is some evidence that genetic factors play at least a part in male crime. Christiansen was able to show that concordance was higher for more serious crime than for minor offences. The findings for female criminals are of interest. They, of course, are much rarer than male criminals. The prevalence was about 2.5% in female twins. Twin concordance rates are lower for female than for male twins absolutely. But in relation to the prevalence they are much higher. MZ partners of female criminals were 13.6 times more often convicted than the average female. And there was a greater contrast between MZ and DZ pairs (13.6 vs. 5.6) than there was in the case of male pairs, suggesting that biological factors make a bigger difference in female crime than in male crime. It is also likely that it requires more environmental stress to make a female break the law than it does a male, and that female offenders have even more unsatisfactory environments than male offenders, as Cowie *et al.* (1968) showed to be so for young female offenders in England.

Adoption Studies

It came as something of a surprise, to me at least, when studies based on adoptees in Denmark also supported the hypothesis of genetic factors in criminal behaviour as a whole. Hutchings' careful study (Hutchings, 1972; Hutchings and Mednick, 1974) was based on a register of 1145 male non-familial adoptions in the Copenhagen area between 1927 and 1941 and on police records. It is of further interest as an illustration of the research strategies using adoptions recently pioneered or extended by Rosenthal and Kety. Table 4 examines the offspring of parents whose criminal status is known, and does so in a cross-fostering design. When the adoptive father was criminal and the biological father not known to the police, the rate was hardly any higher than when neither the biological nor the adoptive father was known to the police. When the biological father had a criminal record and the adoptive father was not known to the police, 21% of the adoptees had a criminal record. The highest rate was found when both the adoptive and the biological father was criminal, possibly suggesting an interaction effect.

Table 5 examines the fathers, biological and adoptive, of criminal adoptees and those of matched non-criminal adoptees. More clearly than in Table 4, this shows the independent influence of both genetic and environmental factors. 70 of the

Table 4. Criminality of adoptees, including results of a cross-fostering experiment (data of Hutchings, 1972)

	Number of adoptees	Percentage with criminal record
Neither father known to police	333	10.4
Adoptive father criminal, biological father not known to police	52	11.2
Biological father criminal, adoptive father not known to police	219	21.0
Adoptive and biological fathers both criminal	58	36.2

Table 5. Fathers of criminal and noncriminal adoptees (data of Hutchings, 1972)

	No. of criminal fathers	
	Biological	Adoptive
143 criminal adoptees	70	33
143 control adoptees	40	14

143 biological fathers of criminal adoptees had a criminal record (49%), compared with 40 (or 28%) of the biological fathers of the control adoptees, suggesting some genetic influence. But there was just as much contrast between the adoptive parents, highlighting the influence of environment. 23% of the adoptive fathers of the criminals had a record, compared with only 10% of controls. Very little of the genetic effect could be explained by associations with mental illness in the families. Nor was there a correlation between subsequent criminality and pregnancy or birth complications of the adoptees. Discussing his findings, Hutchings considers that genetically transmitted characteristics of the autonomic nervous system could to a certain extent account for the apparent genetic influences on criminal behaviour by placing certain individuals at greater risk than others of succumbing to crime.

Confirmation that antisocial behaviour is not purely social in origin comes from an American study by Crowe (1972, 1974). He investigated 46 children of female offenders who had given up their babies for adoption. By the age of 25 there were significantly more arrests and criminal convictions among these index adoptees than in a control group. Personal follow-up investigation showed that 6 of the index group (13%) had 'definite antisocial personality', compared with none of the control adoptees; diagnosis was made blind. In 5 of the 6 antisocial cases the biological father as well as the biological mother had a criminal record. Environmental circumstances such as age at adoption, broken home and psychiatric abnormality in the adoptive parents did not differ significantly between the index and control groups. However, it was interesting that the antisocial index adoptees differed from those index adoptees who were not antisocial in certain unfavourable conditions. Notable among these was the length of time spent in temporary care such as orphanages before final adoption. Although the control group had been equally exposed to the same conditions, they did not develop a high rate of disorder. The findings seemed to point to the importance of interaction between genetic endowment and environmental factors in the development of antisocial personality.

Psychopathic Personality, Alcoholism, Neurosis

The Copenhagen Register of non-familial adoptions was used by Schulsinger (1972) in an investigation of psychopathy—or at least of that kind of psychopathy which comes to psychiatric attention. Psychopathic adoptees were identified through the Danish Psychiatric Register. Psychopathy was defined as inappropriate, non-psychotic, impulse-ridden or acting out behaviour, persisting after the age of 19. This definition secured good agreement between three psychiatrists who rated the records blindly. The incidence of mental disorder in the adoptive

Table 6. An adoption study of psychopathy (data of Schulsinger, 1972)

Mental disorder in relatives	57 Psychopathic adoptees		57 Control adoptees	
	Biological relatives $n = 305$	Adoptive relatives $n = 131$	Biological relatives $n = 285$	Adoptive relatives $n = 133$
Any mental disorder	58 (19.0%)	18 (13.7%)	37 (13.0%)	16 (12.0%)
Psychopathic spectrum disorder	44 (14.4%)	10 (7.6%)	19 (6.7%)	7 (5.3%)
Psychopathy, strict	12 (3.9%)	1 (0.8%)	4 (1.4%)	2 (1.5%)
Psychopathy, fathers only	5/54 (9.3%)	1/54 (1.9%)	1/56 (1.8%)	0/57 (0.0%)

and biological relatives of 57 psychopathic adoptees and 57 matched control adoptees was investigated by means of records. Table 6 shows that the total incidence of any mental disorder was only slightly higher among the biological relatives of the psychopathic adoptees than in the other groups of relatives. The contrast was much greater in respect of psychopathic-like disorders. Schulsinger grouped together into what he called "psychopathic spectrum disorders" cases of psychopathy, of doubtful psychopathy, and of criminality, alcoholism and hysterical character disorder; and these were about twice as frequent in the first group as in any other. Strictly defined psychopathy was mainly a disorder of the male sex. If one restricts the investigation to the fathers of the adoptees, it can be seen that strictly defined psychopathy occurred among 9.3% of the biological fathers in Schulsinger's study and among not more than 1.9% of any of the other groups of fathers.

In alcoholism Goodwin and his colleagues have reported rather surprising findings (Goodwin *et al.*, 1973, 1974). Not only did they confirm the importance of genetic factors, probably fairly specific ones, for alcoholism, but they disconfirmed some widely held environmental theories. Again using the Danish registers they found significantly more alcoholics among the sons of alcoholic parents placed for adoption early than among other adoptees. The incidence of alcoholism in the adopted sons was no less than that found in the sons of the same alcoholic parents who had not been adopted. The rate was about 20%, or close to that reported for the sibs of alcoholics by Åmark (1951) and for their parents by Bleuler (1955). Paradoxically it is to twin studies, and the *disc*ordance rate in MZ twins in particular, that we must turn to obtain a perspective on the importance of environmental factors in the development of criminal behaviour, personality disorder and alcoholism.

Turning from deviance that is largely socially defined to psychiatric disorder as such, I shall be very brief as regards the neuroses and personality disorders. Twin studies have been carried out at the Maudsley Hospital by Slater and Shields (1969) and more recently in a Berlin psychoanalytic clinic by Schepank (1974). Despite different views on the value of depth psychology we agreed that genetic factors played a part in influencing the occurrence and type of many neurotic and personality disorders. Schepank found that the main symptom was alike in 54% of

21 MZ pairs and in 14% of 29 DZ pairs. Hysteria, however, was not a diagnosis that made much sense clinically or genetically in either study. The influence of genetic factors in personality disorders was recently confirmed in Schulsinger's study of psychopathic personality to which I have already referred.

Affective Psychosis

There is no need for me to tell you how views about the endogenous depressive psychoses changed as a consequence of the demonstration of genetic heterogeneity in the important and influential studies by Prof. Angst (1966) at the Burghölzli and Prof. Perris (1966) in Sweden; nor need I do more than mention in passing the potential importance of pharmacogenetics in the affective disorders. What is less clear is just how distinct genetically are the clinically unipolar and bipolar disorders. For example, how frequent are recurrent depressive illnesses in the relatives of circular manic-depressives? Should the unipolar and bipolar affective disorders be further sub-divided into separate disease entities according to age, sex, mode of inheritance, response to drugs, or clinical features, as Winokur and others have suggested? Do sex-linked genes play an important part? And if so, is it in unipolar or bipolar cases? It would take a bolder man than me to answer all these questions. I wish I could present you with some new, critical data on some of these topics. The best I can do is to present a re-analysis of old data which appears to confirm some of the genetic differences between depressive probands with and without manic phases but fails to detect any evidence of sex linkage.

Reanalysis of Slater's (1938) Data

When I translated from German into English Slater's classical paper of 1938 (Shields and Gottesman, 1971) on the parents and children of manic-depressives, I noticed that he had selected his probands according to criteria similar to those of Perris. Cases had to have either at least one clear manic and one depressive attack or three separate depressive or manic illnesses. Although Slater did not analyse his data according to whether the proband had a manic phase or not, he did report how many of his 84 typical probands had pure mania, pure depression, circular illnesses, and manic or depressive illnesses with elements of the opposite phase. It was stated that the case history material had been deposited in the archives of the Deutsche Forschungsanstalt für Psychiatrie in Munich where the investigation was carried out. Dr. Edith Zerbin-Rüdin very kindly searched the archives for me and sent me what could be found. This included clinical summaries for all 138 probands who had children. Those for the 84 typical cases included Slater's classification into depression, circular, etc. All contained brief descriptions of affected parents and children, some of which could be supplemented by information supplied by Dr. Zerbin-Rüdin from other sources. Unfortunately the clinical summaries did not mention the total number of children or the ages of the relatives. This information was given in separate family history sheets, but these were available for only 64 of the 138 families. This meant that Bezugsziffern and morbid risks could not be calculated for the unipolar and bipolar probands or for male and female probands separately. However, in the families for which in-

Table 7. The families of probands with and without mania. Reanalysis of Slater's 1938 data

	Proband			
	Manic or bipolar (86)		Unipolar depressive (52)	
	N	%	N	%
Probands with affectively ill parent or child	39	45	15	29
Total affectively ill parents and children	54		17	
Ill relatives per proband	0.63		0.33	
Ill relatives, female	33	61	9	53
Parents or children:				
Manic or bipolar	16	30	2	12
Unipolar depressive	10	19	5	29
Unclassifiable affective illness	28	52	10	59

formation was available the average number of children (about 3.0) and the proportion of relatives over the age of 50 (about 40%) was similar for probands with and without mania and for male and female probands. Assuming this is also true for the families where detailed information was not available, the groups can justifiably be compared in order to see whether they differ in the number and kind of affected relatives. Affectively ill relatives and the atypical probands who had not been categorised by Slater into depressive and circular groups were classified into bipolar, unipolar or unclassifiable affective illness by a psychiatrist, Dr. John Scott Price, using criteria similar to those of Perris. He did this without knowing the classification of other members of the family.

In the following provisional analysis I have combined together the 12 probands who had recurrent mania and the 74 who were classified as having bipolar illnesses. 45 of these 86 probands were male and 41 female. There were 52 recurrent depressive probands, only 11 of whom were male. Of 71 affectively ill parents and children only 5 had recurrent mania, and these were all relatives of probands with both manic and depressive attacks.

Table 7 compares the manic and circular group with the recurrent depressive group. It confirms Angst and Perris in that probands with manic attacks more often have a family history of affective disorder—45% of probands compared with 29%. The bipolar group had 0.63 sick relatives per proband, the unipolar group only 0.33.

Both Angst and Perris found an excess of female cases among the affected relatives of unipolar probands. Despite the high proportion of females among Slater's unipolar probands we were unable to confirm this. There was actually a slightly smaller proportion of females among affected relatives in the unipolar group—53% compared with 61% in the bipolar.

Of greater interest, however, for the unipolar-bipolar distinction is the type of illness. Considering the inevitable limitations of the data, it is not surprising that a little more than half the affected relatives in both groups were unclassifiable as strictly unipolar or bipolar, usually because they had had only a single attack,

But among those that could be classified, illnesses with manic phases were more frequent than recurrent depressions in the families of the manic or bipolar probands in the ratio of 16:10. In the recurrent depressive families there were 5 unipolar relatives to 2 bipolar. There is therefore certainly some tendency for relatives to have the same type of illness as the proband. In the bipolar families the tendency was even greater than in the case of Angst's study, though not as great as in that of Perris. However, Slater's study shows more relatives with manic attacks in the families of recurrent depressives than either Angst or Perris. There are significantly more bipolar illnesses in the families of bipolar probands.

Sex-Linkage

From time to time the theory of a dominant gene on the X chromosome has been put forward to account for the inheritance of manic-depressive psychosis or part of it. This has usually been in an attempt to account for the excess of female cases. Since females have two X chromosomes and males only one, females are twice as likely to have one with the abnormal gene on it. The theory was shown many years ago to be incorrect for endogenous affective illness as a whole. Too many cases of father-son transmission were observed, as Slater (1938) pointed out. This is incompatible with sex-linked inheritance, since a man transmits his X chromosome to his daughters and his Y chromosome to his sons.

In recent years X linkage has been suggested for one or other of the affective illnesses, unipolar or bipolar. Most recently this has been suggested for bipolar illnesses in the U.S.A. by Winokur and Tanna (1969) and by Fieve *et al.* (1973). This is despite the fact that there is not the same excess of female cases as there is in unipolar depression. But there are of course other possible explanations for a sex difference besides an abnormal gene on the X chromosome.

The evidence in favour of sex linkage in bipolar affective disorder comes from the rarity of father-son transmission found in some studies and from claims that the genetic factor is located on the same chromosome as marker genes for colour vision and the Xg blood group which are of course known to be on the X chromosome. Altogether 15 families have so far been reported in which manic-depression and either the Xg blood group or colour-blindness occur, and the odds are that the two sets of gene are not segregating as independently as they would if they were on different chromosomes. However, the evidence for linkage is not as secure as it is for other conditions.

One difficulty is that the Xg locus is thought to be situated at one end of the X chromosome, while the colour vision loci are towards the other end. The extent of crossing over of genes makes it difficult to detect linkage unless the loci are near one another. It is unlikely that a mood regulating gene would show detectable linkage with both colour blindness and the Xg blood group. There are several conditions, including Becker's muscular dystrophy, which from the mode of inheritance are clearly X linked but in which linkage with either colour vision or the Xg blood group—let alone both—has not been detected (Zatz *et al.*, 1974). It is also worth pointing out that dominant X linkage unlike recessive sex linkage is a rare mode of transmission in human genetics.

Table 8. Parent-child pairs. Reanalysis of Slater's 1938 data

		Proband					
		Manic or bipolar			Unipolar depressive		
		Male	Female	Total	Male	Female	Total
Affectively ill parent or child:							
Male	obs.	13	8	21	2	6	8
	exp.	12.1	8.9		2.8	5.2	
Female	obs.	18	15	33	4	5	9
	exp.	18.9	14.1		3.2	5.8	
Total		31	23	54	6	11	17

The lack or rarity of father-son transmission of bipolar psychosis has not been confirmed in most studies. There was no lack of such cases in Perri's bipolar families, for example (see also Perris, 1971; Goetzl *et al.*, 1974; James and Chapman, 1975). Fieve *et al.* (1973) themselves found 9 instances in their own series and argued that sex linkage may apply only in some cases of bipolar psychosis. But if that were so, it would make linkage all the more difficult to detect. It would be surprising if the manic-depressive families in which colour blindness occurs all happened to belong to the sex-linked type.

Let us now see whether there is any support for sex linkage in Slater's subdivided data. Table 8 shows all pairs of affected parents and children according to sex. Distribution in both the bipolar and the unipolar group is very close to random expectation. In the bipolar group there is no evidence at all for an absence or scarcity of male-male pairs as predicted by the X linkage hypothesis: 12.1 were expected by chance, 13 were observed. In the unipolar group, numbers are small, but again the distribution is very close to what would be expected if there were no association with sex. Together with the evidence from other studies, it therefore looks as if claims for sex linkage should be treated with caution.

Winokur not only separates the unipolar from the bipolar primary affective illnesses (as most of us would agree is justified) but he subdivides the unipolar depressions into pure depressive disease (typified by the late onset male) and what he calls depressive spectrum disease (typified by the early onset female) (Winokur, 1972). In the latter but not in pure depressive disease or in bipolar affective disease there is said to be an excess of alcoholic and sociopathic relatives, particularly males, whereas depressive relatives are predominantly female. In Slater's material alcoholic relatives characterize the bipolar families (14 cases) rather than the unipolar families (3 cases). As depressive spectrum disorders in Winokur's sense I have tentatively counted criminal, psychopathic and hysterical relatives as well as alcoholics. The proportion of such cases per proband (0.31) was the same in the bipolar and unipolar groups. Within the unipolar group the number of such relatives per proband was also very similar for male and female probands (0.27 and 0.32 respectively) and for those with onset before and after age 40 (both 0.31 cases

per proband). There was therefore no support for Winokur's hypothesis. However, it must be pointed out that numbers are small and it is possible that Slater's and Winokur's diagnostic criteria coincide only very loosely.

Earlier in my lecture I referred to the higher risk for relatives of probands of the less frequently affected sex according to one form of polygenic theory. Slater's data tend to support this view. 11 male recurrent depressive probands had 6 affectively ill relatives or 0.55 per proband. 41 female recurrent depressive probands had 11 affected relatives which is only 0.29 per proband. It is unfortunate that numbers are so small and that we were unable to calculate morbid risks.

Conclusions

Let me try to summarise what I found in my provisional reanalysis of Slater's 1938 study of manic-depressives. There was some support for the nosological distinction between unipolar and bipolar disorders. Parents and children of bipolar probands, compared with those of recurrent depressives, suffered from more affective illness and in particular more bipolar psychosis. But illnesses of both types occurred in the families of each kind of proband. Even when one ignores the unclassifiable endogenous affective disorders, correspondence was far from exact. Sex-linked inheritance could be ruled out, since there was no lack of transmission of psychosis from father to son in either the unipolar or the bipolar group. There was no confirmation of Winokur's theory that unipolar depressions should be subdivided according to age, sex and family history of alcoholic and psychopathic disorders. Slater's material has of course many limitations for confirming recent hypotheses concerning heterogeneity and mode of inheritance. I would certainly not claim that our slender observation on depression among the relatives of unipolar probands of the less frequently affected male sex was by itself strong evidence for polygenic inheritance.

In present times we have to learn to live with uncertainty. I think we have to be satisfied with three broad and aetiologically overlapping clinical types of depression: bipolar, unipolar and reactive. I think we should avoid hyperinflation of biologically unconfirmed disease entities. Of the three broad types—I am leaving out of consideration the problematic mixed schizo-affective psychoses—the bipolar type is the least frequent and most "genetic". If there are dominant genes of major effect, the relatively high risk for family members and the low general population risk for bipolar affective disorder makes one think that here is where they might be found. The second type, endogenous depression without manic phases, is commoner. Some cases may be genetically bipolar; others, it seems, are not. Fairly specific polygenic influences on mood may be involved, while personality and life events play a role too. Lastly, reactive depressions, the commonest type. The diagnostic distinction is notoriously difficult (some would say impossible) to make. Some cases so diagnosed may well occur on a similar genetic basis to recurrent endogenous depression as Stenstedt (1966) believed; but most seem to be either non-genetic, like those in our Maudsley twin study (Slater and Shields, 1969; Price, 1968) or only indirectly and non-specifically genetic through influences on personality structure, as in Shapiro's (1970) study of Danish twins with "non-endogenous" depression.

In recent years family studies and drug studies have both helped in the classification of affective disorders, even if we are far from having all the answers yet. Perhaps combined genetic and pharmacological or other biological studies will be of even greater help. Let us hope so.

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