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Correspondence

TYPOLOGIES OF DEPRESSIVE DISORDER BASED ON FAMILY HISTORY OR GENETIC DATA

DEAR SIR,

Through what is essentially a genetic approach to classification, Winokur and associates (Winokur *et al.*, 1971; Winokur, 1972; Marten *et al.*, 1972), following Hopkinson and Ley (1969), recently reported the isolation of two subtypes of unipolar depressive disorder differentiated by age of onset and contrasting family history patterns. These subtypes consist of an early-onset disorder (prior age 40) characterized by *higher* morbidity among relatives, with elevated alcoholism and sociopathy as depressive equivalents, and a late-onset disorder (after age 40) characterized by *lower* morbidity among relatives and the absence of such equivalents, the former representing a 'spectral', the latter a 'pure', form of depressive disease.

For the reviewer, a natural assumption concerning the genetic separability of these subtypes is the expectation that relatives of probands differentially assigned to them will be prone to the identical subtypes and the order of onset to which each corresponds; that is, some correlation between the age of onset in relative and proband must be assumed if each subtype is to be considered genetically viable. This assumption, however, immediately implies an error in the methodology of these studies residing in what would seem to be the logical need to revise risk periods used in the calculation of morbidity risk (MR) estimates (age-corrected prevalences) in the evaluation of family history data. For both the early-onset and late-onset subtypes this refers to the revision of risk periods in accordance with the differential onset limits that circumscribe these separate disorders.

By contrast, the above investigators have generated a typology using a procedure in which the dichotomizing of probands by age of onset is followed by subsequent estimations of MRs with the *full* risk period for affective disorders in general. Contrary to the onset limits imposed upon probands, this procedure implies first that affected relatives are free to vary with respect to age of onset within the full risk period, and second that non-affected relatives are at risk for a disorder well beyond the age limits peculiar to these disorders themselves. Either of these implications, of course, would tend to question the validity of this typology.

Apart from criticizing this methodological point, the main purpose of this letter is to suggest that the *post facto* but logical revision of risk periods argued by the above assumptions involves a paradox in which one basis for separating these subtypes may be significantly lessened. This basis refers specifically to the extent of morbidity among relatives between subtypes, reported as being roughly twice as high in early-onset disorder.

For illustration sake, take MRs estimated through the popular Weinberg abridged method (Slater and Cowie, 1971). Using this method the MR is determined by the quotient,

$$\frac{a}{b-b_o-\frac{1}{2}b_m}$$

where a is the number of relatives affected, b the number examined, b_o the number not yet in the period of risk, and b_m the number in the period of risk. Less the number of affected individuals, the denominator or 'Bezugsziffer (BZ)' is essentially a weighted sum based on the ages of all relatives at the time of examination. For relatives not yet in risk the weight is zero, for those in risk 0·5, and for those beyond risk 1·0. The Table reveals some general

TABLE

Disorder	Revised risk period	Weights Number of relatives			Expected* modification	
		Pre-risk	At risk	Beyond risk	BZ	MR
Early-onset ..	15–40	No change	Decrease	Increase	Increase	Decrease
Late-onset ..	40–60	Increase	Decrease	No change	Decrease	Increase

* Compared with calculations using the full risk period (15–60).

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expectations regarding the modification of MRs (per change in BZ) calculated using revised risk periods for the early-onset (15–40) and late-onset (40–60) disorders *vis à vis* currently reported MRs calculated using the full risk period (15–60, from Marten *et al.*, 1972). For early-onset disorder, relatives between 40 and 60 formerly weighted 0·5 for being in risk, on revision are weighted 1·0 as being beyond risk, increasing the BZ. For late-onset disorder, relatives between 15 and 40 formerly weighted 0·5 for being in risk are weighted zero as being pre-risk, decreasing the BZ. Relative to reported MRs for these subtypes, the effect of revised risk periods on the BZ and inversely on the MR implies a distinct tendency: a *convergence* in the extent of morbidity among relatives between subtypes. This suggests a possible reduction in the weight of evidence for separating affective disorders into these subtypes on the basis of genetic data.

Undoubtedly, the ultimate test of the validity of this typology is conclusive evidence supporting a correlation between age of onset in ill relatives and probands, providing at least that this correlation is not also the effect of environmental variation; e.g. the greater likelihood of life stress factors being involved in rearing by a mentally ill parent among early-onset probands. Such factors could also mediate this correlation if one does in fact exist.

JOE GALDI.

721 Erie Avenue,
Takoma Park,
Maryland 20012,
U.S.A.

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FLUROTHYL (INDOKLON) IN DEPRESSION

DEAR SIR,

Some seven years ago, Rose and Watson introduced into this Department the use of the inhalational convulsant agent flurothyl in the treatment of depressive illness, and published a report on their early experience with this drug (Rose and Watson, 1967). In this they claimed that previously reported undesirable post-ictal effects, such as severe headache, nausea and vomiting, could be avoided by strict control of the dosage and meticulous attention to the technical details of the administration. Since that time, flurothyl convulsant therapy has been available here as an alternative to electro-convulsant therapy; meanwhile clinical studies have continued, comparing flurothyl at first with bilateral ECT and later with unilateral ECT to the non-dominant hemisphere.

In this more recent investigation, the results indicate a statistically significant, and possibly clinically important, therapeutic advantage of flurothyl over unilateral ECT. It is the purpose of my letter to report this finding, preliminary to communication of results of the study in full.

The patients in this trial were mainly out-patients who had been referred for convulsive therapy with a diagnosis of primary depression by the consultant psychiatrists. They were allotted randomly to one or other form of treatment, which was given twice weekly under double-blind conditions. Prescribed antidepressant medication was not altered, so that these patients fell into four groups, according to whether or not they were also receiving drugs.

Assessment of depression by means of the Hamilton scale was made by the independent, blind, rating psychiatrist before treatments began, after four convulsive treatments, and at the end of the course of treatments. The 'course' was not set as any arbitrary number but depended upon the clinical judgement of the individual's psychiatrist as to the value of continuing convulsive therapy. In fact, the number of treatments given ranged from 2 to 16 for flurothyl, with an average of 7·6, and 4 to 17 for ECT, with an average of 8·6. Rating after four treatments was decided on before the trial started as being somewhere near half-way through an average course.

Hamilton Rating Score after 4 treatments

	N	Mean score	Mean improvement score	Mean no. treatments
Flurothyl with anti-depressive drugs ..	30	21.07	16.00	8.3
Flurothyl only	23	23.78	16.00	6.7
ECT with anti-depressive drugs	32	30.59	8.31	9.1
ECT only ..	19	26.1	10.79	7.8

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