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A Twin Study of the Psychiatric Side Effects of Oral Contraceptives

KENNETH S. KENDLER, M.D.,[1,2] NICHOLAS G. MARTIN, PH.D.,[1,4] ANDREW C. HEATH, D.PHIL.,[1] DAVID HANDELSMAN, M.B., B.S., PH.D.,[3] AND LINDON J. EAVES, D.SC.[1]

Oral contraceptive (ORC)-related depression and irritability are among the most commonly reported drug-induced psychiatric symptoms. To investigate the etiological role of genetic factors in ORC-related symptoms, we studied questionnaire responses in 715 monozygotic and 416 dizygotic volunteer twin pairs concordant for ORC usage. Biometrical genetic analysis indicated that the liability to ORC-related depression was clearly influenced by genetic but not familial-environmental factors. Similar, but less definitive, results were found for ORC-related irritability. Multivariate genetic analysis indicated that both the genetic and the individual-specific environmental factors that influenced the liability to ORC-related depression and irritability were largely distinct from those that influence baseline levels of psychiatric symptoms. Genes play an important etiological role in ORC-related psychiatric side effects. The genes that influence liability to these side effects appear to differ from those that are etiologically important in baseline psychiatric symptomatology.

A large body of literature now supports the etiological importance of genetic factors in most major psychiatric disorders (Vandenberg et al., 1986). The field of pharmacogenetics has shown that genes are responsible for much of the wide variation found in populations in the metabolism and excretion of drugs (Vesell, 1978), including those used in psychiatry (Alexanderson et al., 1969). Despite the fact that several drug-induced psychiatric syndromes are common and can be disabling (Guggenheim and Erman, 1985), however, very little is known about the role of genes in these important clinical entities.

In this report, our goal is to clarify the role of genetic and environmental factors in one of the more common and well studied drug-induced psychiatric syndromes: the psychiatric side effects of oral contraceptives (ORCs; *British Medical Journal*, 1969; Fleming and Seger, 1978; Glick and Bennett, 1981; Kane, 1976; Slap, 1981; Weissman and Slaby, 1973). By examining the side effects to ORCs as reported in a large volunteer twin registry, we seek to answer two specific questions: a) To what extent is the liability to ORC-related psychiatric symptoms influenced by genetic and/or familial environmental factors? b) What is the relationship between the genetic and environmental factors that influence liability to ORC-related psychiatric symptoms and the genetic and environmental factors that influence liability to ORC-induced physical side effects and baseline levels of psychiatric symptomatology? This final question addresses the hotly debated issue of whether psychiatric symptoms experienced on ORCs are simply a reflection of baseline psychiatric symptoms or the result of distinct etiological factors (Fleming and Seager, 1978; Grounds et al., 1970).

Methods

Subjects and Scales

Questionnaires were mailed between November 1980 and March 1982 to 5967 adult twin pairs enrolled in the voluntary Australian National Health and Medical Research Center Twin Register. After having sent reminders to nonrespondents, questionnaires were received from both members of 3810 pairs, including 1984 female-female and 907 opposite-sex pairs. Zygosity was assigned on the basis of questionnaire responses, which, in other samples, have been shown to be about 95% accurate (Cederlof et al., 1961; Kasriel and Eaves, 1976; Magnus et al., 1983; Martin and Martin, 1975). As found in other volunteer twin panels, monozygotic and female-female twin pairs were in excess of population expectation (Lykken et al., 1978).

Information concerning many psychological and biomedical variables was sought using the questionnaire. Women were asked several items pertaining to "reproductive history." One of these items was, "Have you EVER used a contraceptive pill?" Those who answered "yes" were then asked, "Did the contraceptive

[1] Department of Human Genetics, Medical College of Virginia/Virginia Commonwealth University, Richmond, Virginia.
[2] Department of Psychiatry, Medical College of Virginia/Virginia Commonwealth University. Send reprint requests to Dr. Kendler, Department of Psychiatry, MCV Box 710, Richmond, Virginia 23298.
[3] Department of Medicine, University of Sydney, New South Wales, Australia.
[4] Dr. Martin's present address: Queensland Institute for Medical Research, Herston, Queensland 4006, Australia.
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pill cause any upset to you or your health?" This question could be answered either by checking "no upset," or by answering "yes" or "no" to the following nonmutually exclusive items: a) weight loss, b) weight gain, c) nausea (feeling sick), d) irregular cycles (breakthrough bleeding, irregular bleeding), e) acne (pimples), f) feeling bloated (swollen), g) depression (sadness), h) irritability (easily upset) and i) other (specify). The abbreviations used in this report for these items are simply the item answer, except that "edema" is used for item f. Genetic analysis is confined to the 1131 female-female twin pairs in which both members reported having ever used ORCs.

The questionnaire also contained the anxiety (A) and depression (D) scales from the Delusions-Symptoms-State Inventory of Bedford et al. (1976) and the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975). The responses of this twin sample to the A, D, and neuroticism (N) scales of the EPQ have been analyzed elsewhere (Jardine et al., 1984; Kendler et al., 1986, 1987). Because of the marked skewness of the raw A and D scores, these variables were transformed before analysis by the function: $\log_{10}(x + 1)$.

Data Analysis

Because the data on the ORC-related side effects were in a discontinuous yes/no format, traditional methods of biometric analysis developed for quantitative traits in twins (Eaves, 1977) were not applicable. Instead, we assumed that underlying each discontinuous variable was a corresponding latent variable (*i.e.*, liability) the distribution of which was continuous and normal. A threshold superimposed on this latent distribution divides the curve into areas corresponding to "no" and "yes" answers. This is analogous to the multifactorial threshold model of Falconer (1965), except that the observed variable is now a dichotomous item response rather than a disease status.

From each two-way contingency table, which cross-classified the response of the first twin by that of the second twin, we separately estimated the tetrachoric correlation (or correlation in liability) and its standard error by the method of maximum likelihood (Heath et al., 1985; Olsson, 1979; Pearson, 1900; Tallis, 1962). The tetrachoric correlation is the correlation between the continuous latent liabilities in each member of the twin pair, where the joint distribution is assumed to be bivariate normal.

Univariate Genetic Analysis

Expected values for the correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs were expressed as a function of the additive effects of alleles at multiple loci (VA, termed additive genetic variance) and the effects of family or shared environment on twin resemblance (EC, termed "common" or "shared" environment). We assumed that EC contributed equally to the resemblance of MZ and DZ twins. The validity of this assumption has been defended elsewhere (Kendler, 1983). Environmental factors that do not contribute to twin resemblance (ES, termed "specific" environment) are not estimated separately, but can be calculated as ES = 1 − VA − EC. Maximum likelihood estimates for VA and EC were derived by fitting models directly to the contingency tables for MZ and DZ twins (Eaves et al., 1978; Kendler et al., 1986). The goodness of fit of different models was compared by the likelihood ratio χ^2 test (Joreskog, 1978). In univariate analysis of same-sex MZ and DZ twins, only one degree of freedom is available for hypothesis testing. That is, a full model estimating both VA and EC is a perfect fit. We were therefore interested in determining whether fitting the model with either EC alone or VA alone resulted in a significant worsening of fit compared with the full model. If the fit of the model deteriorated significantly with one but not the other parameter, then the single parameter model that produced the good fit was to be preferred to the full model on the grounds of parsimony. For some of the items, none of the three models (*i.e.*, VA/EC, EC only, and VA only) could be shown to differ significantly. In these circumstances, one model could not be rigorously preferred over another; however, the full model has the advantage of providing parameter estimates for both VA and EC, thereby permitting a tentative estimate of their relative importance.

Multivariate Analyses

Our multivariate analysis proceeded in two stages. The first was to perform a conventional, or, as we term it, "phenotypic" factor analysis of the product-moment correlation matrix between individual side effects and A, D, and N scores. This analysis was done using orthogonal factors and traditional eigen value criteria followed by varimax rotation (Statistical Package for the Social Sciences [SPSS], 1981). Because members of a twin pair are not independent, we performed two such analyses, one on the first and one on the second member of the twin pairs. We measured the similarity of factor loadings by means of the congruency coefficient (r_c) (Derogatis et al., 1972).

The second stage of this part of the analysis was the performance of a multivariate genetic analysis on these same variables. Whereas the purpose of univariate genetic analysis is the description of the degree to which genetic and environmental factors influence the *variance* of an individual item, the purpose of a multivariate genetic analysis is the clarification of the degree to which genetic and environmental factors are

responsible for the *covariance* between different items (Martin and Eaves, 1977). The approach to multivariate genetic analysis in this paper is to consider it a generalization of factor analysis in which we estimate separate genetic and environmental factors.

For this analysis, we created for MZ and DZ twins separately an 18 × 18 matrix containing both the correlations and the cross-correlations for the six dichotomous side effects and the three continuous measures of A, D, and N. This matrix contained three kinds of correlations: a) correlations and cross-correlations for the six dichotomous side effects in the form of tetrachoric correlations as used for the univariate analysis (Olsson, 1979), b) correlations and cross-correlations between the three continuous measures in the form of product-moment correlations, and c) correlations and cross-correlations between the dichotomous and continuous measures calculated as an approximation to the biserial correlation (Olsson et al., 1982). A biserial correlation represents the correlation between a normally distributed latent trait underlying a dichotomous item and a continuously distributed variable.

Because it was not possible to assume that these matrices were positive definite, we fitted models by a least-squares procedure (Joreskog, 1978; Joreskog and Sorbom, 1983) in which we weighted the MZ and DZ matrices by their respective degrees of freedom. Because standard errors of the approximate biserial correlations were not available, however, it was not possible to further weight the individual correlations within the matrices. Nevertheless, we have found that the estimates of factor loadings from such analyses are quite robust to variations in the method used for weighting; unweighted solutions give estimates quite close to those found with the appropriate weighted solution.[4] Unfortunately, an unweighted analysis does not provide any measure of absolute goodness of fit. If the residual sum of squares (SS) of the most elaborate model, divided by its degrees of freedom (*df*) is regarded as an estimate of error variance, however, then an *F*-test can be used to assess the worsening of fit when a simpler model is fitted, provided that the simpler model uses a subset of the parameters of the more complete model. This criterion is used as a guide to the relative goodness of fit of the various multivariate models; however, it is an approximate test because it assumes that the observed correlations are all independent.

We were specifically interested in testing two broad multivariate models, which we have termed the "common" and "independent" pathway models, respectively (Kendler et al., 1987; Martin and Eaves, 1977). The common pathway model assumes that both genes and environment influence symptom covariation by acting on the same latent variable. For example, genes and environment might both influence a latent dimension, such as "stress-induced depression," which is in turn responsible for the covariation between basal and ORC-related depression scores. The independent pathway model assumes that genes and environment act differently to influence symptom covariation. That is, the pattern of symptom covariation produced by environmental factors acting alone is different from the pattern of covariation produced by genes acting alone. The models were so parameterized that the common pathway model was a specific subhypothesis under the more general independent pathway model (Kendler et al., 1987).

Because the univariate analyses revealed no unequivocal evidence that familial environment played an etiological role for any of the ORC-related side effects, and previous similar results had been obtained for A, D, and N (Jardine et al., 1984), multivariate models were fitted that contained only VA and ES as sources of symptom covariation. After selecting the most appropriate model, the final step was to derive loadings for the nine items on each factor. To provide a unique solution, the loadings for A were set to zero for the second and third genetic and environmental factors; thus the first genetic and environmental factors would extract the common genetic and common environmental variance, respectively, that is associated with baseline psychiatric symptoms. Loadings on ORC-related depression were set to zero for the third genetic and environmental factor so that the second genetic and environmental factor would reflect the common genetic and environmental variance, respectively, associated with ORC-related affective symptoms. (If the genetic [or environmental] differences in liability to ORC-related symptoms are entirely explained by differences in liability to baseline symptoms, then loadings of the second genetic [or environmental] factor should be negligible.) Finally, the third genetic and third environmental factors will account for the remaining variance (*e.g.*, that associated with ORC-related somatic symptoms). These two sets of ("unrotated") orthogonal factors were then separately rotated using varimax criteria (Harman, 1976).

Results

Side Effect Frequencies and Reliability

Of the 4874 female respondents in the sample, 3218 (66%) reported having used an ORC. Side effects of ORCs were reported at the following frequencies: weight loss, 1.8%; weight gain, 36.1%; nausea, 13.8%; irregular cycles, 12.6%; acne, 3.0%; edema, 16.1%; depression, 17.8%, and irritability, 22.5%. The number

[4] Heath, A. C. Unpublished data.

of users reporting the side effects of weight loss and acne were too small to permit meaningful analysis. Therefore, these two items were not further considered.

The reliability of reported side effects to ORCs was assessed in 42 women who had ever used ORCs and who answered the questionnaire twice at an average interval of 3 months. The mean of the tetrachoric correlation between their two responses for the remaining six symptoms was .77 and ranged from a high of .93 for edema to a low of .56 for irritability. The reliability of ORC-related depression was .74.

Univariate Genetic Analysis

Genetic analysis is confined to the 1131 female-female twin pairs (715 MZ and 416 DZ) who were concordant for ever having used ORCs. The tetrachoric correlations for the six side effects to ORCs in these twin pairs and the results of univariate model fitting are presented in Table 1. For all six side effects, the tetrachoric correlation was higher in MZ than in DZ twins. For the results of univariate model fitting, the side effects can be divided into two groups. In the first group, weight gain, edema, and depression, the EC only model could be significantly rejected against the full model by a likelihood ratio of χ^2. However, the VA model could not be rejected and was therefore accepted on the grounds of parsimony. Estimates of VA (*i.e.*, narrow "heritability") for these three symptoms were: weight gain, +.37; edema, +.37, and depression, +.32.

Univariate genetic analysis was less informative for nausea, irregular cycles, and irritability. It was not possible to choose statistically between the three models. However, for all three symptoms, the VA only model provided a modestly better fit than did EC only. In particular, for irritability, EC only (χ^2 = 2.06, p = .151) fit considerably worse than did VA only (χ^2 = 0.00, p = .999). Furthermore, when values of VA and EC were estimated from the VA/EC model, values for EC were uniformly very low whereas values for VA were substantial. For example, with irritability, the VA/EC model estimated EC to be .00 and VA to be 0.32.

TABLE 2

Product-Moment Correlations between OC-Related Side Effects, Basal Psychiatric Symptoms, and Neuroticism[a]

	1	2	3	4	5	6	7	8	9
1. Weight gain		14	10	36	22	17	10	5	13
2. Nausea	9		18	16	26	16	11	6	14
3. Irregular cycles	9	16		14	18	12	11	11	10
4. Edema	32	17	20		30	24	10	6	9
5. Depression	19	23	10	21		45	21	20	22
6. Irritability	17	17	5	21	44		20	15	20
7. Anxiety (DSSI/sAD)	8	12	10	17	18	17		67	60
8. Depression (DSSI/sAD)	9	10	6	16	23	19	69		56
9. Neuroticism (EPQ)	13	9	8	15	28	20	60	59	

[a] Correlations (×100) for the first twin are in the upper triangle and for the second in the lower triangle.

Phenotypic Multivariate Analysis

The first step in multivariate analysis was to produce a correlation matrix for the six side effects on ORCs, neuroticism (N) and the transformed anxiety (A) and depression (D) scores. This was done separately for twin 1 and twin 2 because observations from members of a twin pair were not independent. These two matrices are seen in Table 2.

The next step was to perform a conventional or "phenotypic" factor analysis on these two matrices. We generated orthogonal factors which were rotated to varimax criteria (SPSS, 1981) (Table 3). Three factors were identified in both twin groups. The first factor, which was very similar in twin 1 and twin 2 (r_c = .999), loaded most heavily on A, D, and N. The loadings for ORC-related depression and irritability on this factor, although positive, were small (*i.e.*, <

TABLE 1

Univariate Genetic Analysis of Oral Contraceptive-Related Side Effects

Side Effect	Tetrachoric Correlations				Likelihood Ratio χ^2 tests (df = 1)		Best Fit Parameters Estimates (±SE)	
	MZ		DZ		EC only	VA only	EC	VA
	r	SE	r	SE				
Weight gain	.38	.05	.14	.08	6.28*	.34		.37 ± .05[a]
Nausea	.36	.08	.14	.11	2.58	.10	−.07 ± .24	.43 ± .27[b]
Irregular cycles	.38	.08	.20	.12	1.72	.02	.02 ± .24	.36 ± .28[b]
Edema	.46	.07	.19	.10	4.72*	.10		.45 ± .06[a]
Depression	.43	.07	.10	.10	7.36**	1.10		.41 ± .06[a]
Irritability	.32	.06	.16	.09	2.06	.00	.00 ± .19	.32 ± .22[b]

[a] Best fit parameters are given for VA only model when EC only but not VA only model can be rejected against full model.

[b] For other symptoms, where no significant difference is found in fit for the three models, the results of the full (VA/EC) model are provided. Estimates of EC only and VA only from the single parameter models are, respectively: nausea, .28 ± .06, .35 ± .07; irregular cycles, .31 ± .07, .38 ± .08; and irritability, .27 ± .05, .32 ± .06. 95% confidence intervals can be obtained by multiplying reported standard errors by 1.96. Estimates for ES equal 1 − VA − EC.

* $p < .05$; ** $p < .01$.

TABLE 3
Loadings (×100) of OC-Related Side Effects, Basal Psychiatric Symptoms, and Neuroticism on Varimax Rotated Phenotypic Factors for Twin 1 and Twin 2

	Twin 1			Twin 2		
	I	II	III	I	II	III
1. Weight gain	5	16	56	4	17	38
2. Nausea	7	29	17	7	24	20
3. Irregular cycles	9	21	14	6	6	26
4. Edema	2	28	55	8	12	73
5. Depression	12	78	16	14	76	15
6. Irritability	13	52	15	12	51	17
7. Anxiety (DSSI/sAD)	83	13	8	84	7	13
8. Depression (DSSI/sAD)	78	12	0	80	14	10
9. Neuroticism (EPQ)	69	18	9	68	22	10

.15). The second factor, which was also quite similar in the two twin groups (r_c = .977), loaded most heavily on ORC-related depression and irritability. Modest loadings for physical symptoms reported on ORCs, particularly edema and nausea, were also found on this factor. The third factor, slightly less stable across twin groups (r_c = .946), loaded most heavily on both analyses on two ORC-related somatic symptoms: weight gain and edema.

Multivariate Genetic Analysis

The first step in the multivariate genetic analysis was to determine the adequacy of fit of the most general model. Because the phenotypic factor analysis identified three factors, our initial general model postulated three specific (*i.e.*, nonfamilial) environmental and three additive genetic factors. Furthermore, this general model assumed the independent pathway model outlined above (*i.e.*, that genes and environment could separately influence symptom covariation). Reducing the number of either the environmental or the genetic factors resulted in a significant worsening of fit by the criteria outlined above. For example, the fit of a model assuming only two genetic and two environmental factors was far worse (F = 4.72, df = 14,249, $p < 10^{-6}$) than that of the general model.

The next step was to determine whether the genetic and environmental factors influenced phenotypic covariation by a common pathway. Restricting the model in this way also resulted in a significant worsening of fit (F = 2.22, df = 21,249, p = .002).

Therefore, we report the varimax rotated factor loadings from the best fitting model including three environmental and three genetic factors where these factors could each separately influence covariation between the nine variables (Table 4). Unrotated factor loadings differ little from those found after varimax-rotation, and so are not reported here. The first environmental factor loads strongly only on A, D, and N and contributes little to any of the ORC-related side effects. The second environmental factor loads most heavily on ORC-related depression and irritability, but also has considerable loadings on ORC-related weight gain and edema. The third environmental factor loads heavily on only a single symptom: ORC-related irregular cycles.

TABLE 4
Factor Loadings and Specifics (×100) for Three Genetic and Three Environmental Factor Solution (Varimax Rotated)

	Environmental				Genetic			
	I	II	III	Sp	I	II	III	Sp
1. Weight gain	−3	38	8	69	11	9	59	0
2. Nausea	12	18	28	72	2	39	20	40
3. Irregular cycles	3	8	78	0	10	21	12	56
4. Edema	2	33	21	63	10	30	59	0
5. Depression	8	57	10	47	30	57	12	0
6. Irritability	14	55	1	61	15	54	5	0
7. Anxiety (DSSI/sAD)	64	1	9	49	53	12	9	18
8. Depression (DSSI/sAD)	58	4	4	58	54	10	6	16
9. Neuroticism (EPQ)	45	10	3	53	53	16	9	43

The first genetic factor was similar to the first environmental factor in loading mostly on A, D, and N. For example, although this factor accounted for 29% of the variance in basal depression scores, it accounted for only 9% of the variance in liability to ORC-induced depression. ORC-related depression and irritability loaded highest on the second genetic factor, followed by ORC-related nausea. Edema reported on ORCs was modestly loaded on this factor but weight gain hardly loaded at all (.09). Loadings for A, D, and N on the second genetic factor were quite modest. For example, although this factor accounted for 32% of the variance in liability to ORC-induced depression, it accounted for only 1% of the variance in liability to basal depression. The third genetic factor was characterized by substantial loadings only on ORC-related weight gain and edema.

Discussion

The main results of this investigation can be briefly summarized:

1. In a self-report inventory from a large volunteer twin sample, a substantial proportion of women who reported using ORCs noted ORC-related side effects, of which ORC-related depression and irritability were among the most common.

2. Genetic factors could be clearly shown to play an important etiological role in two physical ORC side effects (weight gain and edema) and in ORC-induced depression. The heritability of liability for these symptoms was in the range of 30% to 45%. No significant evidence for familial environmental influences was found for any ORC-related side effects. The results suggested but did not prove that genetic factors were important in ORC-related irritability.

3. Phenotypic multivariate analysis suggested that ORC-related psychiatric symptoms were nearly in-

dependent of both ORC-related physical side effects and basal psychiatric symptoms.

4. Multivariate genetic analysis indicated that genes and environment act separately in influencing the covariation between the symptoms studied. Genes that influenced ORC-related and basal psychiatric symptoms appeared to be largely distinct. This observation was most clearly demonstrated in comparing ORC-related and basal depression scores. Distinct genes also influenced ORC-related physical and psychiatric symptoms. Although different individual-specific environmental factors appeared to influence ORC-related and basal psychiatric symptoms, similar factors appeared to influence ORC-related depression, irritability, weight gain, and edema.

Implications

From a psychiatric perspective, each of these results is of potential interest. In accord with numerous previous surveys, psychiatric side effects are among the most commonly reported problems associated with ORC use.

Genes were clearly shown to influence ORC-related depression. The results on ORC-related irritability were also most consistent with a major genetic influence. These results suggest that ORC-related psychiatric side effects cannot be attributed entirely to factors such as "suggestion," "scapegoating," and confusion about maternal role (Bakker and Dightman, 1966; Lidz, 1969; Weissman and Slaby, 1973), unless these are themselves genetically influenced. Furthermore, we could detect no impact of common environment in ORC-related depression or irritability. This lack of impact argues against the importance of such factors as guilt related to particular parental values to which both members of the twin pair would be exposed. Just as genetic factors influence liability to many psychiatric disorders that occur without pharmacological precipitation (Vandenberg et al., 1986), genes may also play an important role in determining who will develop drug-related psychiatric syndromes.

However, the univariate genetic analyses were unable to address the question of whether ORC-related psychiatric side effects result from a specific action of the ORC or result only from basal levels of psychiatric symptoms. In fact, several investigators suggest that most psychiatric side effects to ORC simply reflect individuals who, in their baseline condition, are also symptomatic (Fleming and Seager, 1978; Goldzieher et al., 1971). Because baseline symptoms of anxiety and depression appear to be heritable (Jardine et al., 1984; Kendler et al., 1986), this is a plausible hypothesis. The univariate analysis also cannot clarify the relationship between the psychiatric and physical side effects of ORCs. Because weight gain and edema related to ORCs appear to be heritable and women might find such symptoms distressing, it is also possible that ORC-induced depression is heritable *only* because ORC-induced weight gain is heritable.

Conventional factor analysis demonstrated discrete factors for basal levels of psychiatric symptoms, ORC-related psychiatric symptoms and ORC-related edema and weight gain. The relative independence of ORC-related psychiatric symptoms and neuroticism is in accord with some previous work in this area (Grounds et al., 1970). Others, however, have reported contradictory findings (Fleming and Seager, 1978).

Phenotypic factor analysis provides no insight into the relative impact of genetic and environmental factors on symptom covariation. Using genetic multivariate analysis, we first tested whether genes and environment influence the covariation of this set of symptoms in the same way. The answer is that they do not. Therefore, we estimated discrete environmental and genetic factors. The genetic multivariate analysis showed that there is little relationship between the environmental determinants of basal and ORC-related psychiatric symptoms. The genetic factors that influence basal and ORC-related psychiatric symptoms are slightly more closely related, but even here the relationship is weak. By contrast, the suggestion from the genetic multivariate analysis is that, although the genetic factors influencing ORC-related psychiatric symptoms and weight gain-edema are relatively independent, the environmental factors influencing these two sets of ORC-related side effects are substantially correlated.

The results of the genetic multivariate analysis are consistent with the hypothesis that the genetically mediated biological mechanisms that influence vulnerability to ORC-related depression are largely distinct from those that mediate vulnerability to "basal" depression. This finding is consistent with findings that ORC-related depression may result from specific effects of ORCs on tryptophan metabolism (for review, see Parry and Rush, 1979). For example, the genes that specifically influence ORC-related depression without affecting basal liability to depression may influence the impact of ORCs on tryptophan metabolism in the liver, including the apparent subsequent depletion of pyridoxine and the resulting changes on brain levels of biogenic amines. Genes that influence the liability to certain drug-induced syndromes may be *distinct* from the genes that influence the same syndrome when it occurs without pharmacological agents. These results suggest an important difference between ORC and reserpine-related depression. Individuals with a family history for affective illness may be at increased risk for reserpine-induced depression (Guggenheim and Erman, 1985). This suggests that, unlike

what is found with ORCs, similar genes may govern vulnerability to both spontaneous and reserpine-induced depressive syndromes.

The genetic multivariate analysis also suggests that the genes that mediate ORC-related weight gain and edema have little effect on ORC-related psychiatric symptoms. This is not surprising as the physiology of water balance in response to gonadal steroids probably bears little relationship to their effects on the brain mechanisms subserving mood and behavior; however, these results further suggest that ORC-related psychiatric symptoms are not entirely a response to ORC-related physical symptoms.

Speculation about the apparently distinct role of environmental factors in governing basal and ORC-related psychiatric symptoms is somewhat more difficult. We can only conclude with assurance that these factors are not shared by twin pairs. For example, the kinds of life events that influence basal levels of depression may differ from the environmental perturbations that exacerbate ORC-related depression. It is of particular interest that environmental factors appear largely responsible for the covariation of ORC-related psychiatric and weight gain-edema symptoms. It may be here that we see the effects of environmental influences that alter the threshold to reporting side effects. However, whatever these environmental influences are, they appear to have little impact on basal levels of anxiety and depression.

Potential Limitations

Several potential limitations of this report are noteworthy. First, this research is based entirely on self-report symptoms. Although this has been common practice in previous examinations of ORC-related side effects, it must be noted that these results cannot necessarily be extrapolated to clinical syndromes such as ORC-related major depression.

Second, the subjects comprising the twin sample studied in this report volunteered to participate. Although this self-selection may have biased the results, at least for basal levels of anxiety and depression, we know that this twin sample was typical of the general Australian population (Jardine et al., 1984; Kendler et al., 1986).

Third, it was judged impractical to collect information on the specific kind of ORC taken. This makes it impossible in this sample to replicate interesting previous reports relating the frequency of ORC-related side effects to the relative potency of the estrogenic *vs.* progestin content of the pill (Cullberg, 1972; Goldzieher et al., 1971; Herzberg et al., 1970). However, the time period during which these data were collected (1980 to 1982) was before the widespread introduction into Australia of the low estrogen ORCs. Therefore, the variability in estrogenic content of the ORCs widely available during this period was relatively low.

Fourth, approximately one third of the sample of women who reported ever using ORCs stated that they were currently taking these medications. It is therefore possible that the relationship between the basal levels of A, D, and N on the one hand and ORC-related depression and irritability on the other might be in part confounded in these twins. If such a bias were of importance, one would expect substantial correlations between these symptom groups which we did not observe. To ensure that this was not a problem in our analysis, we compared the relevant correlation matrices for twins who were "past" *vs.* "current" ORC users. The correlations did not differ significantly from one another. Apparently, respondents who were current ORC users were discriminating between their current mental state at the time they completed the questionnaire and their experience of ORC-induced side effects that could have occurred any time during ORC usage (which for over 80% of these women was in excess of a year).

Conclusion

This paper sought to clarify, in a large volunteer twin sample, the genetic and environmental determinants of ORC-related psychiatric symptoms. Three results are worthy of emphasis. First, genetic factors appear to influence the liability to ORC-related depression and irritability. Second, similar individual-specific environmental factors influence ORC-related physical and psychiatric side effects. Third, the genes that influence ORC-related psychiatric symptoms are largely distinct from both the genes that influence baseline psychiatric symptoms *and* the genes that influence ORC-related physical side effects.

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