Parents of High Risk Subjects Defined by Levels of Monoamine Oxidase Activity

by Larry B. Puchall, Robert D. Coursey, Monte S. Buchsbaum, and Dennis L. Murphy

Abstract

Thirty-seven parents of probands with low platelet monoamine oxidase (MAO) activity levels and 38 parents of high MAO probands were examined for MAO activity, past and present psychopathology, and reported psychopathology in other relatives. Results showed generally positive and significant correlations between parents' and children's MAO levels, significantly greater rates of "high MAO related" disorders in parents and relatives of high MAO probands and of "low MAO related" disorders and symptoms in parents and relatives of low MAO probands. Support for a two-directional monoamine hypothesis of affective disorders is suggested.

A number of studies have linked reduced platelet monoamine oxidase (MAO) activity levels to various psychiatric disorders, particularly chronic schizophrenia (see review by Wyatt, Potkin, and Murphy 1979), bipolar affective disorders (Leckman et al. 1977), alcoholism (Major and Murphy 1978; Sullivan, Stanfield, and Dackis 1977; Sullivan et al. 1978; Wiberg, Gottfries, and Oreland 1977), and signs of psychopathy (Coursey, Buchsbaum, and Murphy 1979). In addition, some studies (Nies et al. 1971, 1974) found increased MAO activity in depressed subjects, and Schildkraut et al. (1978) found increased MAO activity in patients characterized as having "schizophrenia-related depressive disorders."

Buchsbaum, Coursey, and Murphy (1976) examined the nature and power of this presumably pathogenic biochemistry by selecting a subject sample based solely on their extremely high or low MAO values as measured by a blood platelet assay. These college student volunteers were then examined to see if the psychopathology relationship found in the psychiatric patient samples would be found in this biologically homogeneous sample. If so, the authors reasoned that MAO levels must be related to psychiatric disturbance and not just an irrelevant concomitant of mental disorder. The findings of the study (Coursey, Buchsbaum, and Murphy 1979) tended to confirm the direct relationship between MAO levels and psychopathology. The low MAO males reported a significantly greater number of psychiatric contacts and criminal convictions, as well as more suicide attempts among their relatives. In addition, the low MAO subjects demonstrated more psychopathology and remote associations on psychological tests (Coursey, Buchsbaum, and Murphy, in press).

The present study extends this examination to the parents of the nonpatient volunteers used in that study. A number of studies have provided evidence for the genetic regulation of MAO activity (Leckman et al. 1977; Murphy, Belmaker, and Wyatt 1974; Nies et al. 1973; Sullivan et al. 1979; Wyatt et al. 1973). Thus it was expected that the evidences of psychiatric disturbance found in the low MAO college student population would also be found in their parents and relatives (siblings, aunts, uncles, and grandparents). In addition, based on the findings of Murphy and Weiss (1972), Nies et al. (1971, 1974), and Schildkraut et al. (1978), it was hypothesized that parents and relatives of high MAO probands might

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show greater incidences of depressive disorders.

Methods

Parents of high and low MAO probands were contacted by mail and subsequently by telephone to arrange for an interview. Psychopathology in the parents was assessed using a structured interview, the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1979). The SADS provides information on past and present psychopathology using the Research Diagnostic Criteria (RDC; Spitzer, Endicott, and Robins 1978) to define diagnostic categories, including schizophrenia, bipolar illness I and II, hyperthymic, cyclothymic, depressive, and substance abuse problems. Because we were dealing with a nonpatient population, it was expected that the incidence of actual diagnoses would be quite low. This presumed lack of severity of problems was dealt with in two ways. First, in addition to comparing incidences of individual diagnoses, we decided to group diagnoses into two broader categories which empirically (Brown 1977; Buchsbaum, Coursey, and Murphy 1976; Murphy, Belmaker, and Wyatt 1974; Murphy and Weiss 1972; Nies et al. 1971, 1974; Schildkraut et al. 1978; Sullivan, Stanfield, and Dackis 1977) have been associated with low MAO (schizophrenia; schizophrenia-related diagnoses; bipolar I and II affective disorders, including mania; alcoholism; and antisocial personality) or high MAO (major or minor depression; depressive personality). These comparisons of individual and group diagnoses in parents and relatives were carried out using Fisher’s Exact Test or χ² test when appropriate where df > 1 (Siegel 1956).

Our second approach to mild degrees of psychopathology was to examine the responses of parents to the lead questions for each of the SADS diagnostic categories. These questions inquire about a prominent symptom or behavior relevant to the particular diagnosis (e.g., extended periods of sadness for depression; periods of excessive drinking for alcoholism). If this question is answered affirmatively by the interviewee, the interviewer proceeds to the remainder of the questions in that section to determine whether an actual diagnosis is warranted. Thus, subjects answering affirmatively to lead questions may or may not be given the final diagnosis, but an affirmative answer does give some indication that the interviewee has experienced some difficulty, symptom, or behavior characteristic of the disorder.

The parents were interviewed individually by the senior author and/or a trained assistant either at the National Institute of Mental Health or at their homes. A small payment was offered to each participant. In addition to data from the SADS, information on other relatives (siblings, aunts, uncles, and grandparents of the proband) was obtained from the parents, even though blood samples were not obtained from these other relatives. This information included incidences of depression, mania, psychotic episodes, mental retardation, antisocial acts, suicide and suicide attempts, alcohol and drug abuse, and contact with a psychiatrist. The Pearson coefficient between interviewers’ ratings of individual item scores on the SADS was .82. After the interview data were gathered, the interviewers exchanged protocols and diagnosed them independently. The rate of agreement on diagnoses was 93 percent. In cases of disagreement, the protocol was reexamined and a diagnosis was arrived at by consensus. Interviewers were blind as to the MAO activity level of the parents and their children.

Blood samples of the parents were analyzed for platelet MAO activities using 14C-benzylamine as the substrate (Murphy et al. 1976) and were reported in units of nanomoles benzaldehyde/10⁶ platelets/hour.

Results

Interviewed vs. Noninterviewed Parents. Table 1 presents the number of parents who were contacted and who were able (e.g., because of geographic location) and willing to participate in the study. Eighteen parents of low MAO male probands, 19 parents of low MAO female probands, 19 parents of high MAO male probands, and 19 parents of high MAO females were interviewed. Overall, one or both parents of 64 percent of the probands of the Buchsbaum, Coursey, and Murphy (1976) study participated in the present study. Out of the total group of living parents, 59 percent were interviewed. Reasons parents were not interviewed included inability to locate the proband and/or parent (six parents—i.e., three couples), parent’s residence out of the region (31 individual parents), unwillingness to participate (15 parents), and death of parents (six parents).

Several comparisons were made between interviewed parents and noninterviewed parents based on the information gathered from their sons/daughters from the study of Coursey, Buchsbaum, and Murphy (1979). First, Minnesota Multiphasic Personality Inventory (MMPI) clinical scale scores of probands whose parents were interviewed were com-
Table 1. Number of probands' parents interviewed from original sample

<table>
<thead>
<tr>
<th>Proband group</th>
<th>Both parents</th>
<th>Father only interviewed</th>
<th>Reasons³ mother not interviewed OA U D NC</th>
<th>Mother only interviewed Reasons³ father not interviewed OA U D NC</th>
<th>Number of probands where both or one parent(s) interviewed</th>
<th>Number of probands where both parents not interviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MAO males (n = 17)</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>9 4 1</td>
</tr>
<tr>
<td>High MAO males (n = 17)</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2 1</td>
<td>5 5 4 1</td>
</tr>
<tr>
<td>Low MAO females (n = 17)</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>5 4 1 4</td>
</tr>
<tr>
<td>High MAO females (n = 16)</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Buchsbaum, Coursey, and Murphy (1976).
2 The original sample included four subjects who had been adopted (two low MAO males and one low and one high MAO females). These four subjects are not represented on this table.
3 OA = out of area; U = unwilling to participate; D = deceased; NC = not able to contact proband to elicit consent.
4 The numbers under this heading represent the number of parents rather than the number of probands.

pared with MMPI scores of probands whose parents were not interviewed. There were no significant differences between the probands of interviewed parents vs. those of noninterviewed parents among the low and high MAO groups for either sex on any of the clinical scales. Second, incidences of psychiatric disturbance of several kinds in relatives as reported by probands in the Coursey et al. (1979) questionnaire were compared. There were no significant differences in incidence of psychiatric disturbance of any kind between interviewed and noninterviewed families within any group as reported by probands. However, it is interesting to note that in the low MAO group, although the difference was not significant, the noninterviewed parent subgroup had a greater incidence of suicide than the interviewed group (four vs. two); in contrast, in the high MAO male group, the interviewed parent subgroup showed higher incidences than the noninterviewed group in two categories of disturbance, outpatient psychiatric treatment (eight vs. one) and alcoholism (six vs. two). Although it must be stated very tentatively, it may be that this study is comparing the somewhat healthier portion of the low MAO male group and the somewhat less healthy portion of the high MAO male group. Insofar as this is the case, it would work against confirming our low MAO hypothesis.

Demographic and Background Data. Demographic and general background data were collected on the parents of the high and low MAO male and female probands. The parents of the four groups of probands who were interviewed did not significantly differ from one another on demographic variables such as social class (Hollingshead Index), current use of psychotropic or other medication, current physical illness, or religious and marital status, although the parents of low MAO probands (male and female combined) were still in first marriages significantly more often than parents of high MAO probands (34/37 low vs. 26/38 high; p < .005, Fisher's Exact Test).

MAO Activity Levels of Parents. Significantly lower MAO activity levels were found for the parents of low MAO probands than for the parents of high MAO probands. These differences appear unrelated to platelet counts since there is a lack of significant differences between the mean platelet counts of those groups (see table 2).

The strength of this relationship of MAO activity between parent and
Table 2. Comparison of platelet MAO levels of parents, grouped by proband’s sex and MAO level

<table>
<thead>
<tr>
<th>Proband group</th>
<th>Proband MAO levels</th>
<th>Parent levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range of MAO platelet activity</td>
<td>Mean platelet MAO activity</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low MAO</td>
<td>3.13–7.98</td>
<td>5.66</td>
</tr>
<tr>
<td>High MAO</td>
<td>12.57–22.54</td>
<td>16.39</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low MAO</td>
<td>5.80–10.47</td>
<td>8.15</td>
</tr>
</tbody>
</table>

₁ Two separate determinations of MAO platelet activities (nanomoles/10⁸ platelets/hour) were taken on the probands, and the means of these two values were used for the probands.

² For parents of low versus high MAO male probands, F = 8.45, p < .006.

³ For parents of low versus high MAO female probands, F = 7.05, p < .01.

⁴ No significant difference between parents of low versus high MAO probands.

child can be seen in the product-
moment correlations: father and son, r = .49, p < .05; father and daughter, r = .56, p < .01; mother and son, r = .49, p < .03; and mother and daughter, r = .30, p < .23. To test whether men and women with similar MAO levels had married each other (assortative mating), fathers' and mothers' MAO levels were paired and analyzed. The correlation coefficient was sufficiently low (r = .14) to rule out the possibility of assortative mating for MAO for our sample.

MAO-Related Diagnoses and Symptoms in Parents. As expected, the occurrence of any single diagnosis was so low (no more than three diagnoses per category per group) that diagnostic categories were grouped according to their hypothesized relationship to low MAO (schizophrenia; bipolar affective disorders I and II, including mania and hypomania; alcoholism, and antisocial personality) or to high MAO (major or minor depression; depressive personality). Using these MAO related diagnoses, the parents of low and high MAO probands were sorted into the three categories of no diagnoses, low MAO diagnoses, and high MAO diagnoses. This yielded an overall significant χ² (6.24, df = 2, p < .05). Moreover, table 3 shows that the parents of high MAO probands alone had a significantly greater number of high MAO related disorders than their low MAO counterparts. For the low MAO related disorders, seven parents of low MAO probands carried a low MAO related diagnosis, while only two parents of the high MAO probands carried a low MAO related diagnosis (p < .08).

All diagnoses were of the affective disorder type and none of the schizophrenic variety (see table 3). For both the high and the low MAO diagnostic categories, only one proband had more than one parent carrying a diagnosis.

With respect to major symptoms as measured by the SADS lead questions, parents of low MAO probands had a significantly greater number of affirmative answers to the alcoholism lead questions than parents of high MAO probands. Other differences (e.g., antisocial personality, hyperthymic personality) were in the expected direction, but did not reach .05 significance level.

Reported Psychopathology in Relatives. Relatives of high MAO male probands were reported by the parents to have a significantly greater incidence of depression than relatives of low MAO males, although the reverse was the case for relatives of female probands (table 4). Relatives of low MAO probands were reported to have higher rates of “mood swings” (dramatically alternating moods of elation and depression) than their high MAO counterparts. When individual illness categories were collapsed into a low MAO related category (mood swings, mania, alcoholism, or antisocial behavior), the number of relatives of low MAO males having at least one of these disorders was significantly greater
### Table 3. Summary of major psychopathology comparisons for low and high MAO parent groups

<table>
<thead>
<tr>
<th>SADS diagnoses</th>
<th>SADS lead questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low MAO related diagnoses</strong></td>
<td><strong>High MAO related symptom questions</strong></td>
</tr>
<tr>
<td><strong>Low MAO related symptom questions</strong></td>
<td><strong>High MAO related symptom questions</strong></td>
</tr>
<tr>
<td>Sex of proband Parents of low MAO probands ($n = 37$)</td>
<td>M</td>
</tr>
<tr>
<td>Parents of high MAO probands ($n = 38$)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

$^*p < .04$; $^{**}p < .025$.

Note.—The numbers in the above table represent the numbers of persons carrying diagnoses and the number of persons responding positively to relevant lead questions. The numbers in the footnotes below represent actual diagnoses or lead questions answered positively. A single person can have more than one diagnosis and answer more than one lead question positively.

1 Diagnoses were made in the following categories: Hypomania (1 low), bipolar II (2 low, 1 high), alcoholism (4 low, 1 high), and antisocial personality (1 low). One person carried two diagnoses. There were no schizophrenia-related diagnoses.

2 Diagnoses were made in major depression (1 low, 5 high), minor depression (2 high), and depressive personality (1 low, 1 high).

3 Positive responses to lead questions for mania (3 low, 3 high), hyperthymic (3 low, 3 Ngh), alcoholism (7 low, 1 high) and antisocial personality (5 low, 1 Ngh).

4 Positive responses to lead questions for depression (11 low, 10 high) and depressed personality (4 low, 5 high).

Sex Differences. Mothers, regardless of MAO group, had a significantly greater incidence of depressive disorders than fathers ($p < .04$). There were no significant sex differences among other first and second degree relatives of the probands for any illness category, though females were reported to have more depression, suicides, or suicide attempts, while males were reported to have higher rates of alcoholism and antisocial behavior.

**Discussion**

This study focused on two aspects of the relationship between MAO activity levels and psychiatric disorders: the possible genetic transmission of vulnerability via MAO activity levels and the psychiatric consequences of that vulnerability.

With respect to the genetic transmission of the MAO activity levels, the correlations of MAO levels between parents and children are compatible with genetic transmission, but they do not rule out the fact that family members have certain environmental, psychological, and non-MAO biological factors in common which may affect MAO activity level and thus produce a significant correlation. Nevertheless, these correlational findings are consistent with the results of three other studies which found significant correlations in normal twins (Nies et al. 1973; Murphy, Belmaker, and Wyatt 1974; Winter et al. 1978). They are also consistent with studies that report reduced MAO levels in well relatives of bipolar patients (Leckman et al. 1977) and in the well twins of schizophrenics in a monozygotic twin study (Wyatt et al. 1973). Further, our mean MAO activity levels for relatives of the male probands in the upper and lower deciles, 8.32 and 12.95, are very similar to those obtained in relatives of alcoholic probands in the lowest and highest deciles, 8.3 and 11.3, by Sullivan et al. (1979). While our data show familial influence, no specific pattern of inheritance was revealed. While there are some recent data from somatic cell hybrids that the structural gene for the catalytic sub-
unit of MAO-A is on the human X chromosome (Pintar et al., unpublished data), the fact that our mother-son correlations were not higher than the father-son correlations does not offer support for this X-linked regulation, at least not for platelet MAO-B activity.

The second aspect of the present study focused on the psychiatric diagnosis and symptoms which have been hypothesized to be related to MAO activity levels. The study found that low MAO parents tend to have higher rates of alcoholism than their high MAO counterparts. Past studies (e.g., Major and Murphy 1978; Sullivan, Stanfield, and Dackis 1977; Wiberg, Gottfries, and Oreland 1977) have found low MAO activity levels in alcoholic subjects; but their methodology was unable to rule out the possibility that alcoholic consumption reduced MAO activity rather than that low MAO levels were a predisposing factor in the development of alcoholism. The present study, however, increases the likelihood that low MAO activity and illness-free histories than those of high MAO females, and the reverse was the case for antisocial behavior. Thus it appears that MAO as an etiological factor in these disorders most likely works in conjunction with other factors, and that there are probably etiological pathways to these disorders that do not involve MAO.

Nevertheless, our overall view of the findings is that they offer positive, although weak, support of monoamine hypotheses of affective disorders. The explanations which might account for the limited nature of these findings fall into two general categories: methodological and biochemical.

Methodologically, at least three factors were operative which would tend to have reduced the power of our findings. First, we may have sampled the healthier families. The low MAO group, especially, may represent a somewhat healthier portion of the original set of low MAO families from the Buchsbaum, Coursey, and Murphy (1976) study since four of those original families in which a suicide had occurred were not available for interviews. Secondly, normals who are not seeking help and who do not feel they are disturbed tend to give socially desirable responses to questions about psychological disturbance. Despite the overall cooperation given by our sample, the interviewees tended to be reluctant to describe the details of their own psychiatric histories and were often poorly informed about the histories of their relatives. That the results were obtained despite the risk of false negatives adds some additional weight to the findings. Lastly, by sampling from a college
population, we may have selected low MAO individuals who but for an exceptionally stable and healthy family (e.g., fewer divorces than expected, Coursey, Buchsbaum, and Murphy 1979) would not have attended college.

A second set of biochemical factors also may have reduced the power of the findings. First, MAO levels in the parents were not so extreme as those of probands. Thus, whatever power the biochemical variable has in accounting for these disturbances, this power was likely substantially reduced by the more average levels of MAO activity found in the parent groups when compared with the original probands. Secondly, extreme MAO activity alone is clearly not the necessary and sufficient condition for affective disorders, and its relationship to psychiatric diagnoses is undoubtedly modified by other biological and environmental factors.

Finally, a note should be made about the pattern of sex differences found in this study. The incidence of the various psychopathologies by sex tended to follow trends established in previous studies. Male parents and relatives generally had higher, though not always significantly higher, rates of alcoholism, antisocial behavior, and mood swings or hypomania than females, and females were generally reported to have more depressive disorders. In addition, there was the reverse of expected results for the relatives of female probands where relatives of low MAO probands were reported to have more depressive disorders than relatives of high MAO probands. These particular sex differences have been commented on elsewhere (Coursey, Buchsbaum, and Murphy, in press; Donnelly et al. 1979).

In conclusion, this study offers positive but weak support for the wider monoamine hypotheses for the affective disorders, but also supports the notion that even a monoamine imbalance is probably only one source of vulnerability to affective disorders. Future research might be most productively aimed at exploring what specific behaviors, affects, and symptoms are related to MAO activity levels. Further, we must reiterate the fact that the existence of a correlation between platelet MAO and diagnoses does not indicate the mechanism by which a blood cell factor may be related to a brain factor, the way the biochemistry becomes translated into a set of behavioral and emotional tendencies, or how these tendencies become suf-

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Table 4. Reported disorders in relatives grouped by MAO group and sex of proband

<table>
<thead>
<tr>
<th></th>
<th>Mood swings</th>
<th>Depression</th>
<th>Mania</th>
<th>Psychosis</th>
<th>Alcohol abuse</th>
<th>Drug abuse</th>
<th>Antisocial</th>
<th>Suicide attempts</th>
<th>Suicide</th>
<th>Brief psychiatric evaluation</th>
<th>Mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MAO</td>
<td>6*</td>
<td>4*</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>(n = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High MAO</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>(n = 138)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low MAO</td>
<td>2</td>
<td>11&quot;</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1*</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>(n = 107)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High MAO</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>(n = 116)</td>
<td></td>
<td></td>
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<td></td>
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</table>

*p < .05. **p < .01.
ficiently pronounced to be brought to the attention of a psychiatrist.

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Acknowledgments

The following people contributed to this project: Dr. Eleanor Dibble, Carolee Freeze, Nancy Garrick, Dr. Elliot Gershon, Ann Marie McLaughlin, Carole Miller, Cathy King, and Norma Whetzel. In addition to the support from the Intramural Research Program at NIMH, this research was supported by a grant from the Computer Science Center at the University of Maryland.
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Booklet on Premorbid Adjustment

A five-part review article Premorbid Adjustment in Schizophrenia: Concepts, Measures, and Implications, by John S. Strauss, Ronald F. Kokes, Rafael Klorman, and James L. Sacksteder, has recently been reprinted. Single copies are available free of charge from the Center for Studies of Schizophrenia. Multiple copies will be supplied to requesters who wish to use the review for teaching purposes.

Aspects of the topic that are covered in the review include: The Concept of Premorbid Adjustment; Measuring Premorbid Adjustment—The Instruments and Their Development; The Relationship of Demographic and Diagnostic Factors to Measures of Premorbid Adjustment; Some Biological Approaches to Research on Premorbid Functioning; The Implications of Findings for Understanding, Research, and Application. The review was originally published in Schizophrenia Bulletin, Vol. 3, No. 2, 1977.

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