

Schizophrenia: An Evolutionary Advance

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INTRODUCTION

Huxley, Mayr, Osmond, and Hoffer (1964) presented a hypothesis that schizophrenia is a genetic morphism (see Huxley, 1955). This is in general agreement with the proposition that all genetic characteristics which exist in a population at a frequency higher than can be maintained by mutation alone must be a morphism. The frequency of the morphic gene is the result of a balance between its selectively favorable and unfavorable properties. An advantage of a morphism is that it allows populations depleted by natural difficulties or disasters to reproduce rapidly when environmental conditions become favorable. A condition which remains a genetic morphism for a long time could eventually become universal if there was a major shift in factors favoring such a development. Hypoascorbemia (Stone, 1965, 1966) may originally have been a genetic morphism, but today after many million years no man can synthesize ascorbic acid and everyone has the Orthomolecular condition hypoascorbemia.

Whenever reasonable statistics are available, they show a lifetime incidence of schizophrenia of about 1 to 2 percent in all racial and ethnic types in all geographical regions. A few studies have shown a higher incidence in lower socioeconomic strata, but if this is a real phenomenon it is not general.

It will be shown later that this might be a true finding and related not to the stress of poverty from a psychological point of view, but to the malnutrition and perhaps increased consumption of bread and sugars which is a natural concomitant of poverty. The diet would also contain less of the more expensive high-protein and high-vitamin foods. Poverty was said to account for the higher incidence because of the psychological stress. In the same way many claims have been made that maternal deprivation causes growth retardation in infants. Whitten et al. (1969), in a carefully controlled experiment on underdeveloped infants, discovered that in spite of assurances from mothers they were feeding their infants adequately, they were not getting enough food. When the infants were provided proper meals in hospital or at home without disturbing the mother-child relationship, these infants rapidly gained weight. Emotional deprivation played no role in growth retardation. Maternal neglect of proper infant feeding was solely responsible. The 1 to 2 percent lifetime incidence, according to Wender (1969), may be an underestimate as it is based upon mental hospital admissions. It does not take into account patients seen in clinics and by private psychiatrists. An estimate of up to 3 percent may be much more accurate.

Another real possibility is that schizophrenic patients who do not recover find it difficult to compete with normal

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people. They must, therefore, work at jobs which pay less or survive on social welfare. This would force them into areas with lower living standards. In addition, unusual behavior may be more acceptable in the lowest income groups.

The evolutionary disadvantages of having schizophrenia are well-known. If the disease strikes before puberty, males are less likely to marry and reproduce. This seems to be less important for females who, if left in the community, have reproduced more quickly. When the disease struck during the child-bearing age, it used to effectively remove most of the patients from the community and prevent a normal reproductive life. The modern concept of treatment in the community makes these restrictive measures much less effective.

Another disadvantage is the high suicide rate which Osmond and Hoffer (1967) have estimated to be about 25 times higher than that in the general population.

In spite of the tremendous effort society has made to limit reproduction of schizophrenics by incarceration in institutions, by therapeutic abortions, and by sterilizations, the lifetime incidence of schizophrenia has remained constant. There is substantial evidence that the newer discharge policies have removed a major reproductive disadvantage and we should expect a real increase in the lifetime incidence; that is, if we combine the lifetime incidence of 1 to 2 percent with the lifetime incidence in offspring of parents now in the community who formerly were kept in institutions, it is inevitable that there will be a real and major increase. Erlenmeyer-Kimling et al. (1966) compared the reproductive rates of 1934 - 36 to 1954 - 56 admissions. The rate increased from 57 to 94 children per 100 patients. They concluded that "any selective disadvantage which schizophrenic illness may have in terms of its evolutionary history is now in the process of disappearing."

There are two main types of compensatory advantages:

1. Physiological

These are reviewed by Huxley et al (1964). They include resistance to surgical and wound shock, to visceral perforation, to high doses of histamine, insulin, thyroxine, and adrenalin, to pain, to arthritis, to many allergies and to many infections.

Carter (1968) examined the relatives of schizophrenics in comparison with similar relatives

of non-schizophrenics in two geographically separate practices in England. Carter selected each schizophrenic patient in these two practices. The control case was the next same-sexed patient in the case files born in the same five-year period. They located 28 schizophrenics who had 64 relatives, and 29 controls who had 73 relatives. There was a definite deficit of virus infections (influenza, measles, mumps, chicken pox, rubella, herpes zoster, common cold, corneal ulcer, plantar warts, and enterovirus infections) among schizophrenic relatives - 58 compared to 95 among controls. There was no difference in the incidence of bacterial infections.

In one of the practices, schizophrenic relatives had a smaller accident rate than control relatives.

Carter also found evidence which supported earlier findings of a diminished susceptibility to allergies. Of great importance was Carter's finding that schizophrenic relatives had an increased pregnancy wastage (miscarriages, stillbirth, and neonatal death rates) and childhood mortality (sex not given); but this was more than compensated by a 30 percent increase in fertility. Fifty schizophrenic relatives had 131 children compared to 79 children on 40 control relatives.

Perhaps these factors accounted for the finding by Erlenmeyer - Kimling (1968) that female offspring of schizophrenic parents (male or female) had significantly lower mortality to age 15 than the population at large. They say "even a slim differential in the probability of reaching childbearing age would be important in the balance of selection relating to schizophrenia."

2. Reproductive advantages

Although schizophrenic males do not marry at the same rate as normal men, the increased fecundity of schizophrenic women and certain psychological advantages of the illness, in an evolutionary sense, more than compensate for this. Over the past two years I have been impressed with (1) the number of schizophrenic women who become pregnant before marriage because they wish to, in response to delusions or because they are not in control of their activities, do not adopt birth control measures, and who in seeking male companionship to break their loneliness will have relations which they do not enjoy as a way of retaining their male friends; (2) the number of adopted children who are schizophrenic brought in by their normal parents. I have the feeling that normal parents who adopt must find out whether either parent was schizophrenic so that if the child becomes ill they can take appropriate action. The prophylactic use of niacinamide, 1 gram per day, is indicated.

GENETICS OF SCHIZOPHRENIA

For many years clinicians, who have worked closely and for long periods of time with schizophrenics and their relatives, have been impressed with the frequency with which they find several members of the same family afflicted with this disease. I have been impressed over the past 18 years, on a case material of over 2000 schizophrenics, with the high degree of association. Not only was it obvious to me, but once the patients had recovered and became knowledgeable about schizophrenia, it was equally clear to them. I have dozens of examples of schizophrenic mothers correctly spotting their offspring who were showing the early signs and symptoms and who, on chemical assay, were found to have malvaria. Invariably, mothers brought in their sick children first for examination. I have numerous examples of young schizophrenic men and women who, upon recovery, brought in sometimes reluctant fathers or mothers who were and had been psychotic many years. I have a few examples where recovered patients brought in their schizophrenic spouses. In fact, it is rare to find families where only one member is ill. As early as 1685, Thomas Willis observed, "It is a common observation that men born of parents that are sometimes wont to be mad will be obnoxious to the same disease."

Genetic theories have shared the field with

environmental theories with fashion rather than fact determining which will be most popular. The earliest environmental theories were the demoniac possession theories which gave way to medical theories when schizophrenia was removed from the sphere of influence of priests and taken over by physicians. During the height of enthusiasm for genetics, it once more was considered primarily somatic or genetic. But by the end of the last war, when psychoanalysis became so influential in the U.S., family theories once more became popular even though there was no new data to support this point of view. Family hypotheses which seemed plausible soon were assumed to be real, and large schools of family therapy sprang up in which the schizophrenic member was considered not the sickest member of a healthy family but the healthiest member of a sick family who had taken upon himself the role of sacrificial lamb. The proponents of this school vigorously attacked the geneticists by demanding a degree of purity and virtuosity of their methods and data hardly ever attained in any branch of medical research even though they had no hard data to support their own point of view.

However, their critique did encourage a series of well-planned studies which, while adding little new information to that gathered by men like Kallmann, Slater, Rudin, Luxenburger, and Schulz, did impress even hard-core environmentalist research centers like N.I.M.H. However, it is impossible to measure the total loss to schizophrenia research by the diversion of immense sums of money to this line of research which added so little new information.

Wender (1969) has summarized the evidence derived from genetic studies:

(1) Consanguinity Studies - as a general rule the closer the biological affinity, the higher the concordance rate for schizophrenia. Rainer (1962) gave the following expectancy of schizophrenia amongst schizophrenic relatives.

| | <i>Percentage Expectancy</i> |
|---|------------------------------|
| General Population | 0.85 |
| Half siblings | 7-8 |
| Full siblings | 5-15 |
| Parents | 5-10 |
| Children (of one schizophrenic parent) | 8-16 |
| Children (of two schizophrenic parents) . . . | 53-68 |
| Fraternal twins | 14 |
| Identical twins..... | 86 |

(2) Family and Psychodynamic Studies- It has been shown that schizophrenics often come from disturbed families. But this fact does not help one decide whether the disturbance in the family resulted from having to live with a schizophrenic or whether it caused the schizophrenia. Wender concludes that this kind of data does not permit the evaluation of the relative contribution of heredity or environment. It is difficult to visualize a family which can avoid being disturbed when one of its close members is ill with schizophrenia, especially when parents are directly or obliquely accused of making their child ill. It is rare to find families who are not disturbed, but in nearly every case the independent variable is the schizophrenia in the sick member, and the dependent variable is family discomfort. As the schizophrenia subsides, so does the degree of family disturbance decrease until it regains its normal pattern when the patient has recovered.

Evidence which favors the major influence of heredity (and minimizes environmental factors) may be summarized as follows:

(a) **Evidence that the illness** can occur during early infancy when it is inconceivable the infant could perceive or respond to schizophrenogenic mothers:

Thus, Bender (1955), Bender and Helme (1953), Fish (1957), Fish and Alpert (1962) have been able to detect abnormal states of consciousness and muscle tone in infants age one month who later clearly were schizophrenic.

These studies begun in 1952 have shown that neurological changes are present as early as one month after birth. Many different changes were found, including a lag or a peculiar sequence of

motor development, or confused proprioception and perception of form, or abnormal torpid or flaccid muscle tone. Fish and Alpert (1962) carefully followed development of states of consciousness and muscle tone in 13 infants born to schizophrenic mothers in state mental hospitals. Four showed marked apathy and irritability and three showed less extreme deviations from the norm. The quiet infants had decreased motor impulses, responded little to proprioceptive stimuli, and in extreme cases had flaccid muscle tone and irregular postural development.

Pollin et al. (1965) studied identical twins (three female pairs and two male pairs) of whom only one was schizophrenic. They found that the twin to become schizophrenic weighed less at birth, was perceived by parents as vulnerable, and therefore received more care and attention. Early development was slower, and this twin always tended to be more dependent and had greater difficulty achieving any degree of autonomy and separateness.

My conclusion differs from the authors who tended to see it as a defect in the mother as she reared her children. I believe the twin destined to become schizophrenic was in fact more vulnerable, that this was correctly perceived by the mother, who, as most mothers would, was forced to give this child more attention and received fewer compensating rewards. This is also true when a child, not a twin, becomes schizophrenic and is compared to normal sibs. I have many families where parents have shown similar solicitude and care for their sick children until the children recovered. After that the parent-child relationship became the same for the schizophrenic child as it had been for the other sibs.

Some, who give unusual prescience to babies, have fallen back on orphanage data to prove that even infants can detect rejection. But recently it has been shown that rejection and malnutrition often go hand in hand, and that marasmic babies properly recover very quickly without huge doses of love (unless of course they equate food and love, but then this is not how psychologists who believe in the importance of maternal rejection would see it).

Studies have been done to detect what were the early malignant influences and whether differential parental attitudes could be detected which would explain why a certain son or daughter became ill. In two investigations, it has been shown that the child who became schizophrenic was more dependent and the family had to make allowances for it. With identical twins, Pollin et al. (1965) observed that the lighter, physically less developed twin developed schizophrenia first.

In a recent study, Block (1969) compared the parents of schizophrenic, neurotic, asthmatic, and congenitally ill children. Block found no support for the idea that there was any psychogenic specificity between these groups of mothers. On the basis of clinical descriptions of so-called schizophrenogenic or asthmatogenic mothers, factors characteristic for each were compared in this empirical test. The mothers of asthmatic children did not differ significantly from mothers of the schizophrenic children. However, not surprisingly, there was an association between parental Psychopathology and symptoms in the child. The correlation was 0.539 which means that the mothers' Psychopathology could account for about one quarter of the psychological symptoms in their children. This is significant, but hardly exciting, and suggests that even a complete removal of all psychiatric symptoms from mothers of schizophrenic children would not relieve their children's schizophrenia appreciably,

(b) **Adoption studies** seem particularly useful in sorting out genetic and environmental factors in the development of schizophrenia. There are four possible combinations, children from schizophrenic parents adopted by either schizophrenic or normal parents and children from normal parents adopted by either schizophrenic or normal parents. One would expect the highest incidence of schizophrenia and other psychiatric problems amongst the group of children from schizophrenic parents adopted by schizophrenic parents, since not only would genetic loading act but also all the presumed stresses of

adoption and separation from biological parents would interplay with the stress of being reared by schizophrenic parents. Next, in order of frequency, would be children from schizophrenic parents raised by normal parents. If there were in fact no significant differences between these two groups, this would be evidence against any major effect of environment in producing schizophrenia. Children from normal parents raised by schizophrenic parents should have a low incidence of schizophrenia while in the last group one would expect the usual 1 or 2 percent lifetime incidence. If these latter two groups were not significantly different this would also be evidence against environmental causal factors.

1. **Children from schizophrenic parents adopted and reared by schizophrenic parents.**

Higgins (1966) selected 50 children out of 200 born from schizophrenic mothers. They were divided into two groups of 25 each using carefully matched variables. One group remained with their mothers their entire life. The other group was separated by age 1¹/₂ and was reared by normal mothers. Higgins had predicted that the group reared by schizophrenic mothers would show greater maladjustment. But the results of the study showed there was no difference between the two groups. The slight differences which were found suggested that rearing by a schizophrenic mother has less to do with the child's level of adjustment than with the direction of its basic orientation to the world. In other words, the mother had little to do

with the fact of the presence of abnormality, but not surprisingly did have some effect on the content of the changes. The Higgins study does not provide data on children of schizophrenic parents adopted by schizophrenic parents but it is the closest to it of any study I have seen so far.

2. Children from schizophrenic parents reared by normal parents.

Karlsson (1966, 1967) selected a group of siblings of schizophrenic patients still in hospital with one parent having a history of mental illness. They had all been reared by normal parents. Out of 119 cases, 17 were schizophrenic. In a further study, Karlsson selected eight other cases who had been reared in a foster home. Karlsson then identified 29 biological sibs and 28 foster sibs. Out of 29 of the biological sibs, six were schizophrenic. None of the 28 foster sibs became ill.

Heston (1966, 1970) examined a series of children of schizophrenic mothers who were reared in foster or adopted homes. Out of 47 cases, five were schizophrenic and another eight were borderline. Thus, about one-third developed major pathology which is comparable to the proportion who develop similar pathology when reared by their own schizophrenic parents. In Heston's control group of children from normal parents reared by normal parents, there were no cases of schizophrenic or of borderline schizophrenic states. Heston also found that another 13 cases presented other psychiatric diagnoses. In the control group there were only nine cases with personality problems. Finally, Heston found that among index subjects who were mentally normal there were a large number of very talented people.

Rosenthal et al. (1968) found similar frequencies of abnormality. Out of 39 index cases, three became schizophrenic and 10 were borderline. Out of 47 control cases none became schizophrenic, but six were borderline. Karlsson (1967) has compared biological relatedness and whether cases were reared by schizophrenic or by normal parents.

His results are shown in Table 1.

Table 1

OFFSPRING OF SCHIZOPHRENIC PARENTS

Reared by Schizophrenic Parent

Monozygotic twins (1)..... Concordance very high

Two Schizophrenic parents . . Risk of developing

schizophrenia 35%

Sibs of schizophrenia —
one parent Risk 12%
One schizophrenic parent. . . Risk 12%

Reared by Normal Parent

Monozygotic twins (1)..... Concordance very high

Two schizophrenic parents . . Only one case found — he is schizophrenic

Sibs of schizophrenia —
one parent 3 out of 9
One schizophrenic parent... 11 out of 100

3. Children from normal parents reared by schizophrenic parents.

Kallmann (1946) found that step-children of schizophrenics did not show any elevated risk of becoming schizophrenic. I have been unable to find any other reports.

TWIN STUDIES

The largest series of twins with schizophrenia were studied by Kallmann (1946), which included 174 monozygotic twin pairs. The most striking findings were that expectancy rates were 14.5 percent for dizygotic twins and 86.2 percent for monozygotic twins. Similar results were reported by Inouye (1961) and Slater (1953). The Kallmann studies have been most extensively criticized but it was shown by Shields et al.(1967) that the criticisms were minor or invalid. Their final conclusion was that "he did not allow himself to be biased," and the data constituted an important source of information to all who would try to unravel the contributions of heredity and environment

to the etiology and phenomenology of schizophrenia.

(1) Identical twins reared in separate homes from infancy.

Gottesman and Shields (1966) reviewed schizophrenia in twins over 16 years of consecutive admissions, and again found concordance rates to be much higher for monozygotic twins, but concordance was related to severity of the illness. Chronic patients residing in or admitted to long-stay hospitals showed the highest concordance.

One of the major criticisms of Kallmann's data by Rosenthal (1961) was that his data contained too few opposite-sexed twins. Generally one would expect an equal number of both types of twin pairs. In the five studies listed by Rosenthal the ratio of opposite sex to same sex varied from 1.54 to 1, to 0.75 to 1. But Kallmann's series included 517 pairs of twins as against 33 pairs in Luxenburger's study. Rosenthal suggested that Kallmann's data could be due to bias by hospital personnel in discovering twins (opposite-sexed twins would be missed) or in calling many pairs dizygotic when in fact they were monozygotic. Shields et al . (1967) reexamined Kallmann's data and methods of data collection and concluded these criticisms were not sound. This is not surprising since Rosenthal provided no experimental evidence for his speculations, i.e., that monozygotic twins in mental hospitals are less frequently missed.

There is an explanation for Kallmann's higher incidence of same-sexed twins. If Kallmann's series, because of its size or for other reasons, included a larger number of twins born to schizophrenic mothers who were ill, one might expect the differential effect of the mother's schizophrenia or sex of offspring to account for this. If in only 20 percent of the theoretical opposite-sexed twins the male was reabsorbed leaving only one female, one could expect an uneven distribution of opposite and same-sexed twins. The same effect would occur in male same-sexed twins and this should increase the ratio of female same-sexed twins to male same-sexed twins. In fact, except for the Gottesman and Shields (1966) study, most twin studies showed an excess of females over males.

Kallmann's unusual distribution of alike and opposite-sexed twins may therefore be the correct one.

Ancillary Evidence

Another line of evidence comes from conditions which are generally accepted as wholly genetic. If it can be shown that these conditions are highly correlated with schizophrenia, then it strengthens the evidence for the genetic basis of schizophrenia. Total finger ridge count is one of the few conditions which is almost wholly genetic.

Mellor (1967) compared finger ridge counts of normal and schizophrenic men and women. He found a significant difference between normal and schizophrenic males, but not between normal and schizophrenic women. There was a significant difference between normal men and women (men having higher counts), but not between schizophrenic men and women. Schizophrenic men had effeminate counts.

FAMILY STUDIES OF MALVARIA

In 1961, Irvine (1961), Hoffer and Mahon (1961) reported that a larger proportion of schizophrenics excreted a mauve-staining factor than any other group. Since then many thousand cases have been examined and the following proportion from various diagnostic groups have been found to be positive.

| <i>Group</i> | <i>Percent Positive</i> |
|---|-------------------------|
| Schizophrenia | |
| (a) First attack..... | 90% |
| (b) During any relapse | 75% |
| (c) Chronic..... | 50% |
| (d) HI over 20 years and in state hospitals . . | 10% |
| (e) Schizophrenics who have recovered ... | 0% |
| (f) Depressions | 25% |
| (g) Neuroses..... | 25% |
| (h) Behavioral disorders and alcoholism .. . | 25% |

(Table continued)

- (i) Adult retarded population in a state hospital65%
- (j) Infantile Autism 0%
- (k) Mentally normal and physically ill 11%
- (l) Normal5%

The mauve factor was not due to dietary factors and only one tranquilizer, mellaril, interfered. So far, there have been no reports failing to corroborate when our method was used as described.

In 30 families where one member was found to have the mauve factor, every other member of the family was tested and information on each person tested was obtained by clinical examination of every adult and by description of parents of their children's behavior. We have found that parents who are well are good observers and reporters.

From the first-order relatives of the index malvarian, 30 percent were also malvarian. This group included 26 schizophrenics, 29 other psychiatric illnesses, two retarded children, one physically ill child, and four who were normal. The nonmalvarian group contained four schizophrenics, eight other conditions, three retarded children, and 44 who were normal. These results are shown in Table 2.

Table 2

| Schizo-phrenia | and | | Well |
|--------------------------------------|----------|-----------------|------|
| | Schizoid | Other Diagnosis | |
| Malvarian | 26 | 31 | 5 |
| Not malvarian | 4 | 11 | 44 |
| Offspring from schizophrenic parents | 13 | 13 | 21 |
| Offspring from normal parents | 0 | 9 | 41 |

Mauve factor is kryptopyrrole (Irvine, Bayne, and Miyashita, 1969).

Comparison with Heston's data shows that the malvarian group, although selected differently, resembles his group of offspring from

schizophrenic parents more than the other group while the nonmalvarian distribution is more like the offspring from normal parents (1966).

From families with one parent malvarian, 40 percent of the children were malvarian. To test the ability of mothers to detect illness in their children, they were asked to bring in urine specimens first from the child they considered the sickest and last from the child they considered most normal. Of the 19 children first tested, 15 were positive. Of the 44 children brought in last, none were positive. If we compare the first three choices against the last four choices, Chi square is over 2.6.

We have been able to test two identical twin pairs. They were so alike physically that their parents often could not distinguish one from the other. All four were malvarian.

The A Twins (born 1939)

DA. had been deeply depressed and anxious for two weeks. A previous depression in 1963 lasted six months, and responded to antidepressant medication. During this time, D.A. was paranoid, believing people were always watching him and talking about him because they knew he was mentally ill. He was also suspicious of his wife. His HOD scores were Total 49, Perception 9, Paranoid 4, Depression 16; and on the EWI (El-Meligi and Osmond, 1970), on a retrospective test, he showed a severe schizophrenic reaction with depression and paranoid ideas. He was started on nicotinamide 3 grams per day, ascorbic acid 3 grams per day, and an antidepressant. Two weeks later, he was nearly well and has remained well since on the vitamins. His HOD scores were Total 10, Perception 2, Paranoid 0, Depression 1, and on the EWI profile he was well.

E.A., his brother, was normal. When infants, his mother tied a ribbon on one so they could be distinguished. Both grew up with similar interests and hobbies. Both are married. E.A. had one convulsion in 1959. The EEC one week later was normal. He took anticonvulsant medication several

years. Between 1962 and 1967 he took dilantin and phenobarbital whenever he became very tense and excessively tired - about five times per year.

The B Twins (born 1951)

This family was discovered when the oldest son, a student at university, became schizophrenic in 1957. He recovered on nicotinamide 3 grams per day. Then he expressed concern about his psychotic father who had been treated several times in a mental hospital. He considered his twin sisters were well although they were having difficulty in school.

I.B. was the smaller of the twins. She resembled her sister but they were always distinguished by size. I.B. was a B average student in school but in grade 11 her performance dropped perceptibly as follows: December average, 52 percent, January average, 43 percent, and in April, 1968, 44 percent.

I.B. tried very hard to overcome her defect, but even though she worked very hard she could not learn. Apart from irritability and shyness, Irene appeared normal. She was started on nicotinamide 3 grams per day. Four months later, her mother reported that Irene had improved markedly. Irene wrote, "Since I have been taking them I found it easier to learn and understand the teachers. I wasn't as crabby as before. I find it easier to talk to people. In school I've improved in five out of eight subjects."

Miss B.B. was considered normal by her parents, but they had been concerned about a deterioration in performance at school. She was a B average student and was able to maintain this record, but had had to study longer hours and it was much harder for her. Both girls had nearly identical HOD scores as shown below.

| Score | Per-Total Score | ceptual Score | Paranoid | Total Score |
|-------|-----------------|---------------|----------|-------------|
| I.B. | 13 | 2 | 0 | 2 |
| B.B. | 13 | 2 | 1 | 2 |

The HOD test is a simple card sort test

developed by Hoffer and Osmond (1961), Kelm et al. (1967), for assisting in the diagnosis of schizophrenia. High scores indicate severe Psychopathology. Normal scores are as follows. Total score, 0 - 30, Perceptual score, 0 - 3, Paranoid score, 0 - 3, Depression score, 0-3.

She was also started on nicotinamide 3 grams per day with no expectation of change. However, three months later her twin in a report wrote, "Before Bev started to take the pills she could hardly talk. She has improved in school and passed into grade 12."

The father had identified himself as a schizophrenic by reading up on it. Born in 1915, he was reasonably well until 1962 when he admitted himself to a mental hospital complaining of severe abdominal pain which he knew was cancer. He was very paranoid about his wife, believing she was having an affair with a neighbor, and he spent much time and energy searching for evidence. His second son, he was convinced, was not his. He was also very anxious and fearful of death. He had no insight and judgment was poor. One month later, he was discharged better, but readmitted a few weeks later for another short stay in hospital. He responded to tranquilizer medication which he continued to take as an outpatient. However, he remained irritable, hostile, unreasonable, and often paranoid, and this resulted in a perpetual marital discord leading to several separations. The hospital diagnosis vacillated between depression and schizophrenia.

The malvarian data resembles the family data reported by other investigators. However, the main error in this work is that the mauve factor may disappear when the schizophrenia becomes chronic, or it may appear only on certain days. If the two diagnostic groups, schizophrenia (a clinical diagnosis) and malvaria (a laboratory diagnosis), were to be combined, it is highly likely the study of the genetics of schizophrenia would be simplified. Our data suggests that malvaria detects borderline or incipient schizophrenia.

Identical schizophrenic and malvarian twins, some of whom were treated with the megavitamin B3 approach. Several years ago, Burrell and Osmond (1959) suggested that identical twins ought to be used for clinical trials since this would both simplify and reduce costs of these trials. Beveridge (1950) had recommended this be done by using one twin as a control. In animal experiments involving butterfat yields, one pair of identical twin cows was as valuable as results obtained from two groups of 109 cows each. For measuring growth during the first year of life, one pair of identical calves gave results equivalent to at least 25 pairs of ordinary calves. When this suggestion was made, no therapeutic studies with twins had been reported nor have any appeared since. The statement made by Burrell and Osmond is still relevant today.

"This is a strange oversight, because it seems that twin pairs used in this way might be of even more relative value than in those animal experiments to which we have already referred. In pure breeds of livestock, one would expect that there would be a greater degree of genetic homogeneity than among humans and so relatively less benefit would be gained by the experimenters. Not only are humans inherently more variable, but also the type of inbreeding which is possible among cattle is socially prohibited, and so more control would be gained by twin studies involving humans. Naturally, this would have to be confirmed experimentally."

There is no direct evidence to show how many subjects per group in a controlled study would be equivalent to one identical twin pair, but by using animal data one could assume that it might be equivalent to 50 subjects per group. Since few clinical studies report more than 50 per group, due to costs and other factors, and since a comparison group of over 30 is usually sufficient to yield significant differences between treated and untreated groups if in fact the treatment is superior, it would follow that one identical twin pair in a therapeutic trial would be just as helpful and much more practical to study

than the usual comparison groups.

In addition, if identical twins responded the same way to similar therapy, this would reinforce the genetic and biological view. If each twin pair represents a study equivalent to comparison groups of 50 subjects each, a series of twins would represent very substantial data equivalent to hundreds of patients.

I have been in direct contact with five pairs of twins of whom two were concordant. Because the patients were examined very early and were mostly young people, this is probably an underestimate. In the B pair, the twin considered well improved substantially on nicotinamide medication. The evidence is strong that had she not started she would have become ill like her sister. In the case of the K. twins, one was never seen but her history of dropping out of school, of stealing and lying was a mini version of the schizophrenic twin's behavior. Of all the seven pairs, four were concordant. From the four adult twin pairs, concordance was present in three pairs. A summary of the twins' history is shown in Table 3 and in the brief case histories which follow.

Mrs. M.G. (Born 1921)

The patient remained well until 1950 when three months after the birth of her first child, a girl, she developed severe schizophrenic psychosis and remained in hospital six weeks. Then she remained well for two years. After that, for the next 14 years, she had to return to hospital fifteen times, the last admission in 1946 when it was recommended that she have a lobotomy. Her average stay in hospital was about one month. She received standard therapy including psychotherapy, drugs, and ECT. Early in 1966, she consulted a family physician for pain in her back. He diagnosed her schizophrenia and started her on nicotinic acid 1 gram t.i.d. She responded quickly and has remained well. I saw her in September, 1966, when she had been well for six months. She was last seen in August, 1969, and was still well. This is the longest period of health since her first attack.

Mrs. M.G.'s son had always been considered retarded. He was started on nicotinamide and after a year was a B-average student in high school and had matured a lot.

Her twin sister, Mrs. L. C, became ill three months ahead of Mrs. M. C. and has suffered similar recurrent episodes of psychosis. She has required fewer admissions but each one has averaged three months. By fall, 1966, she had remained out of hospital five years but was living a sheltered, seclusive, withdrawn life with her husband) Mrs. M. G had made strenuous attempts to persuade her sister to take nicotinic acid but was blocked by her sister's psychiatrist who refused to consider it.

In fall, 1967, this twin again went to a hospital and after one month with no response was going to receive another series of ECT. Her normal sister wrote, "It just breaks my heart that even now they won't try this nicotinic acid."

As girls these twins were so alike it was impossible for friends and relatives to tell them apart.

Mrs. A. Ka (Born 1920)

Patient became schizophrenic in 1956, a few months after the birth of her last child, a boy. In 1960 she was admitted to a psychiatric ward where she displayed visual and auditory hallucinations, thought disorder, and marked apathy. She was given 20 ECT, tranquilizers, propylthiouracil, and nicotinic acid, 1 gram t.i.d. Upon discharge, the patient was much improved, showed little confusion, had no perceptual changes, and was more appropriate socially. She was placed on maintenance nicotinic acid, 1 gram per day, for two months. This is a totally inadequate maintenance dose.

She was admitted several times to another ward. On September 16, 1965, she was admitted for two weeks to start slow-release medication as she had been unable, because of her illness, to take medication. She has continued to function at home since, on home care, with a nurse making regular visits

1. Over the past five years she required about 12 admissions. to give her injectable tranquilizer. Her present condition, chronic schizophrenia, improved but with recurrent attacks of agitation. There are many marital and home problems.

Mrs. M. Ka, the twin, has also been schizophrenic for many years and presented a picture similar to that of Mrs. A. Ka. She has been on home care many years and has received ECT and tranquilizers. However, she has remained a chronic schizophrenic — improved, with many family and marital problems.

The D twins (born June 14, 1949) Linda, at birth, weighed 4 lb. 3 oz. and Lorraine 5 lb. 2 oz. For a long time, the parents could not differentiate the twins. They were slow to walk. At age nine months they began to speak a few words, but after having whooping cough, they both stopped talking to anyone else but to each other, babbling in what the parents called Chinese. Then they began to talk to others more clearly. Both have a peculiar lisp we have noted in several young schizophrenics. Both were slow in school and were considered retarded.

Linda completed grade seven, then quit. In 1959, she felt that she had rocks in her stomach. In 1965, she became disinterested in school, refused to study, and stopped reading because whenever she read she got severe pain in her head. She was admitted to a hospital for severely retarded patients for evaluation and training. There she was found to have a low normal intelligence and was referred to a psychiatric ward for two months. A year later she began to feel she was losing her mind. In 1969 she had a few perceptual changes, suffered thought disorder (blocking, paranoid ideas) and poor judgment, and she was very nervous and tired. She was admitted for a series of unilateral ECT and chemotherapy and was discharged five weeks later improved. Since then, she has continued to improve on nicotinamide 3 grams per day.

Lorraine had a very similar history. She

completed grade seven, but that year she became aware of her breathing and has since been unable to take her mind off this. She became very fearful of dying and for several weeks before admission was too frightened to fall asleep and stayed up continually. She suffered many perceptual changes including visions, feelings of unreality, a feeling her mind was floating away, and hyperawareness of her respiration. She had thought disorder including blocking, paranoid ideas, poor memory and concentration, and confusion. She was also depressed and suicidal. She received a series of unilateral ECT plus the megavitamin B3 therapy, and on discharge was improved.

The K twins (Born June 1950)

Miss A. K. did not believe that she was ill. She was referred because she was charged with stealing. In spring, 1967, while in grade 10, she dropped out of school in order to get married. Her sister Alice also dropped out for the same reason. A. K. hoped to get a job to earn money for her marriage. In the fall, she broke the relationship and became deeply depressed, but in March, 1968, she felt better. For several years, she had been shoplifting and lying to her parents as did her twin sister. She became unreliable, drank heavily, and swore at her parents. They described a character change from a good girl to her present personality. She denied perceptual changes, but on the HOD test admitted many. She also was paranoid, blocked, unreliable, showed poor judgment, and lacked insight. There was no improvement on medication and she was admitted for 5 ECT. March 27 to April 5, 1968, she was better on discharge. After this, she was seen several times and remained better. She left home, worked for awhile, but continued to have trouble with her parents. When last seen in August, 1969, she was on her way to Vancouver for a job, having been kicked out of her home by her parents. Since then, she has been in hospital several times, has continued to drink heavily and has not been replaced on megavitamin therapy.

The mother was seen several times and was the most likely transmitter of the schizophrenic genes. She was puritanical, rigid, hostile, eager to be rid of her children, and most reluctant to take them back.

The twin has not been seen but married recently.

HOD scores were:

| | |
|----------------------|----------------------|
| <i>Per-</i> | <i>Depres-</i> |
| <i>Total ceptual</i> | <i>Paranoid sion</i> |

| | <i>Score</i> | <i>Score</i> | | <i>Score</i> | <i>Score</i> |
|---------------|--------------|--------------|--|--------------|--------------|
| March 5, 1968 | 53 | 15 | | 4 | 14 |
| May 8, 1968 | 100 | 21 | | 6 | 11 |
| June 9, 1968 | 68 | 14 | | 2 | 8 |

The Bu Twins

Both boys were normal until October, 1963. Both were freshmen at university. In the fall, B. began to phone home frequently with great anxiety. He could not study and did not turn in his assignments. At midterms he made a B average. In January, 1964, B. ran away and tried to enroll in the navy (against his religion), but was persuaded to go back to college. In February, B. dropped out and began seeing a psychiatrist. B. remained somewhat better all summer and remained under psychiatric care. In the fall, it was decided that the twins were too dependent on each other and must be separated. It was stated that they suffered from an identity crisis. This was done and the other twin, R., was sent to live with a relative. By November, B. had deteriorated. He argued frequently with his father, told his mother he was in love with her. Later, he read the Merck manual on schizophrenia and told his mother this was what he had.

From January to May, 1965, B. could not keep a job as he fought with every employer. He continued to receive therapy. In May he was admitted to Sheppard Pratt hospital. In the hospital he became very hostile toward his parents and did not wish them to visit anymore. The psychiatrist in charge reported that this hostility was a sign of progress. In September he ran away, but was persuaded

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to return. March, 1966, B. ran away again but was returned by the police. In April, 1966, B. would no longer speak to his father. In September, 1966, B.'s parents asked the hospital to start B. on niacin as their son R., after three months on megavitamin therapy, was much improved. This was refused. October, 1966, B. was taken home and he was started on megavitamin B3 therapy by another psychiatrist. Between January and March, 1967, B. began to improve and got a job delivering books and magazines. In April, 1967, B. developed infectious hepatitis. All medication was stopped and B. quickly regressed until he was violent and psychotic. He was admitted to a local hospital and given nicotinamide and a tranquilizer. Within 24 hours, he was rational and after awhile the tranquilizer was discontinued.

During the summer of 1967, B. was able to work regularly, but tired easily and required a lot of sleep. B. had no regression at any time and slowly continued to improve.

B. often denied that he was ill and would stop taking his medication, but his parents would persuade him to start and he would recover again. September, 1967, the dose was doubled to 6 grams per day and followed by a marked improvement. Last report, January, 1969, he was still improving and was a resident at a special hospital where he took courses.

R., the other twin, was well until March, 1964, when he began to sleep excessively and began to miss classes. He passed in May, but seemed withdrawn. He seemed to be in a daze. He was started on Elavil, but remained depressed and dazed. In September, he became delusional and paranoid and was admitted to a hospital for ECT. This was stopped in October with no improvement. January, R. came home from the hospital, but was very sleepy and behaved irrationally at times and continued to hear voices. By January, 1966, R. seemed better. June, 1966, R. began to receive nicotinic acid 3 grams per day. He improved very quickly and remained much improved and by January, 1969, he was nearly normal. He had a job which he enjoyed. In the spring, 1967, he also developed infectious hepatitis. He was given

nicotinamide up to 6 grams per day and did not relapse as had his brother B.

Table 3

| Condition before | Treatment | Given | Present Condition |
|--------------------------------|-----------|----------------|--|
| Twins personality known to us | | | |
| A | iII | Megavitamin B3 | Normal |
| A | Well | None required | Normal |
| B | iII | B3 | Well |
| B | Well | B3 | Improved compared to initial condition |
| D | iII | B3 | Much improved |
| D | iII | B3 | Much improved |
| M.G. | ill | B3 | Well |
| S.G. | ill | Standard | iII |
| K | iII | B3 | Well |
| K | Well | None | Well |
| Twins treated by others | | | |
| B | iII | B3 | Much improved |
| B | iII | B3 | Much improved |
| A.Ka | iII | Standard | iII |
| M.Ka | ill | Standard | iII |

Of the seven twin pairs, 11 twins were schizophrenic. Of these 11, three received only standard treatment (tranquilizers and ECT) and remain chronic schizophrenics in the community and live in a family torn by marital discord, (Ka twins), or in a hospital enclave created by a devoted husband in their home. The other eight are well or much improved. One of the twins considered well when first seen was much better after three months on nicotinamide medication. Thus, in this small series of seven identical pairs, with no exception, the patients who were treated with the standard therapy were benefitted little, and those receiving megavitamin B3 therapy are well, recovered, or much improved. In each case, the twin first receiving megavitamin B3 therapy recovered first.

**EFFECT OF SCHIZOPHRENIC PARENTS
ON
CONGENITAL ABNORMALITIES AND ON
SEX RATIO OF THEIR OFFSPRING**

It is strange that several decades of research into genetics and familial aspects of schizophrenia have failed to recognize an amazing effect of maternal active schizophrenia on the offspring. Shearer et al. (1967) found that out of 343 babies born to schizophrenic women patients in Michigan's six state hospitals between 1925 and 1964, 148 were male and 186 were female. Even more remarkable was their observation that 14 females and no males were delivered to women whose schizophrenic symptoms came on within one month of the theoretical date of conception. The authors suggested that the mother carried a chemical which interfered with viability development of the Y-chromosome carrying sperm or the fertilized ovum but was not lethal later in gestation.

Taylor (1969) examined the sex of offspring resulting from 54 pregnancies in schizophrenic women admitted to Manhattan State Hospital. There were 49 full-term births — 20 male and 29 female. Of 13 women who became schizophrenic within one month of conception, all delivered female children. Taylor also suggested that the mothers had a toxic blood factor which caused reabsorption of the male fetus if it occurred during the first month, and caused the male fetus to develop abnormally or die slowly if it attacked during the second and third month. Taylor also found that of 13 women who became psychotic within two months after parturition, two delivered females and eleven males. He suggested that schizophrenia developing late in pregnancy is fended off by production of steroid sex hormones by the fetus. When the baby is born, this protective effect is gone and the psychosis is allowed to appear (as if a protective chemical [drug] were suddenly withheld).

This hypothesis suggested that a male fetus in the second and third trimester would prevent or ameliorate schizophrenia in the mother, i.e., that schizophrenic women carrying male fetuses would improve and that schizophrenia would occur in women primarily with female fetuses. This was tested by Taylor and Levine (1969) and found to be true. A study of charts at Metropolitan State Hospital (New York) showed that of 18 pregnancies associated with maternal psychosis, 17 were associated with birth of a female. In pregnancies in which maternal illness improved, all

delivered male offspring; and in pregnancies in which the illness got worse, all delivered females.

Hoffer and Osmond (1960) had already suggested a relationship between pregnancy and schizophrenia. They described how some schizophrenic patients improved clinically during pregnancy especially during the last trimester. They had suggested this was due to increased formation of Ceruloplasmin which would suddenly be withdrawn after parturition. Ceruloplasmin is able to bind toxic substances such as adrenolutin, etc. This could explain the sudden onset of puerperal schizophrenia. However, Taylor and Levine's observations suggest that Ceruloplasmin plays a small role if any and that the steroid hormones probably are the effective chemicals.

As will be shown later, this effect of pregnancy on schizophrenia may have a profound effect on racial survival, for schizophrenic women who have experienced the feeling of well-being associated with being pregnant may seek to repeat this condition more often, and those mothers giving birth mainly to girls may continue to become pregnant until they give birth to a boy.

Rosenthal (1966) listed the offspring from three published studies: (1) by Kahn, (2) by Schultz, and (3) by Elsasser. There seems to be no apparent relationship between schizophrenia and sex ratio of the offspring. But if one divides the schizophrenic mothers into those first admitted at age 35 or earlier and into a group admitted at age 36 and older, there is a trend toward the same sex ratio found by Shearer et al. and by Taylor. The younger women are more apt to be both pregnant and schizophrenic while the older

group would be more apt to have their children before the onset of their schizophrenia. Out of about 70 babies born to the under-35 age group, about 30 were male and 41 were female. But from the over-36 age group, out of about 75 children, 45 were male and about 30 were female. If one examines the mean age of first admission of all women for the three studies, it is found that the mean age for the Kahn group was about 42 years, and for the Schultz group about 39. The mean age for the Elsasser group is about 33. One would, therefore, expect a similar sex ratio divergence between the Kahn, Schultz group on the one hand and the Elsasser group on the other. In fact, this is the case. In the latter group, only the women admitted under age 35 gave birth more often to females while the women over age 36 gave birth more often to males.

In the past two years, I have treated 121 women who were schizophrenic and who had given birth to at least one child. On a routine first interview the names, ages, and general condition of all the children born to the patients were listed. It was thus possible to relate in a crude way the onset of each attack of schizophrenia, if there were more than one, to the pregnancies and the sex of the children. The onset of schizophrenia, unless it is very sudden, can very rarely be accurately related to time, and in most cases there is a large error in the estimate. The sex ratios of the offspring were examined for offspring born before the first attack of schizophrenia, and after the disease had appeared. The results are shown in Table 4.

Table 4

SEX RATIO OF OFFSPRING BORN TO MOTHERS BEFORE AND AFTER DEVELOPING SCHIZOPHRENIA

| | Offspring born before schizophrenia appeared | Offspring born after schizophrenia appeared | Total |
|--------|--|---|-------|
| Male | 154 | 192 | 38 |
| Female | 91 | 167 | 76 |

The difference is significant (Chi square over 30). There are two major differences: (1) The increased proportion of females which supports the findings of Shearer et al. (1967), and Taylor and Levine (1969). This difference from the expected normal ratio is also very significant (Chi square over 6). (2) The increased proportion of males born to the women who had not yet become schizophrenic. This is significantly

different from the expected even ratio (Chi square over 7). This unexpected finding is supported by the Elsasser data recorded by Rosenthal. It suggests that even before the woman becomes schizophrenic her body provides an environment chemically hostile to female fetuses (or female-producing sperm). Over the entire child-bearing years, there still remains a higher ratio of male to female than would be expected in a normal population.

A striking example from our series is one woman schizophrenic who, before she married, continually heard voices and saw visions until treated with megavitamin B3 therapy three years ago. She had seven girls. Of these one is severely retarded, one has epilepsy, and two have chronic schizophrenia.

Of the women seen, 11 were treated with megavitamin B3, and after recovery gave birth to 12 children, eight male and four female. One woman gave birth to one child during her schizophrenia and another child while on treatment with nicotinic acid.

The finding that women who are going to become schizophrenic give birth to more male babies is puzzling. Perhaps this is due to the protective effect of male fetuses and comparable to recurrent doses of preventive medication. A woman potentially schizophrenic becoming pregnant with a male fetus would be given a protective period which would decrease her chance of becoming schizophrenic for a period of time. If she had two or three successive male pregnancies, this would postpone the disease even more. But eventually the pressure for the disease would no longer be contained and the disease would occur.

The conclusions from the studies reviewed in this section are: (1) that women destined to become schizophrenic give birth to more boys than girls; (2) that women already schizophrenic give birth more often to girls; (3) that male fetuses protect mothers from and ameliorate any schizophrenia which may be present. Early medication with megavitamin B3 restores normal sex ratios among offspring of schizophrenic women.

It has been known for some time that the incidence of congenital abnormalities among offspring of schizophrenic women is about three times the normal incidence. Taylor found that out of 49 children born, six had birth defects (deafness, mutism, cerebral palsy, blindness, and retardation). If we consider the mute and retarded child to be infantile schizophrenics, it leaves a very high proportion of congenital defects.

**RELATIONSHIP OF CONGENITAL
ABNORMALITIES
(teratogenic activity)
TO NICOTINIC ACID OR NICOTINAMIDE**

Landauer (1957) showed that 3-acetylpyridine, an antimetabolite of vitamin B3 (nicotinic acid or nicotinamide), is teratogenic for chicken embryos. It produced skeletal muscle hypoplasia. Nicotinamide given at the same time completely protected the embryo against the teratogenic effects of 3-acetylpyridine. This report initiated a series of studies on so-called nicotinamide antagonized teratogens. Caplan, Zwilling, and Kaplan (1968) found that 3-acetylpyridine produced degenerative effects of myoblast cultures and greatly stimulated production of cartilage in chondrogenic cell cultures. This was prevented by nicotinamide, which by itself inhibited cartilage formation. They suggested that nicotinamide may participate in differentiation of limb structure by sustaining muscle formation and inhibiting excessive cartilage formation. The teratogen 3-acetylpyridine acts, therefore, by interfering in the nicotinamide control of growth.

Roger et al. (1964) found that the teratogenic effect in chick embryos of certain organophosphate insecticides was prevented by nicotinamide and several of its derivatives (like NAD) and analogues. As well as being teratogenic, these substances were also neurotoxic. As little as 30 mg of nicotinic acid and nicotinamide per egg protected the embryo. NAD was even more active. Tri-o-cresyl phosphate produced neurotoxic changes in adult hens including marked ataxia and debilitation.

Nicotinamide and phenyl nicotinate prevented most of the changes.

Nicotinamide and analogues also protected chick embryos from teratogenic effects produced by eserine, insulin, 6-aminonicotinamide. The last compound produces behavioral changes in dogs such as hyperexcitability, hyperthermia, uncoordinated movements, and twitching of the ears and cheeks. It produced lesions in the anterior horn of the spinal cord and in the brain stem nuclei. Three-acetylpyridine also produces specific lesions in the hypothalamus (Hick, 1955). Nicotinic acid derivatives protected against neurotic effect of several substances (Chambers and Casida, 1967).

The best known teratogen is thalidomide which, according to Jarvik (1962), produced deformed babies in 20 percent of the women who took it. A few women also developed neuropathy. Frank et al. (1963) found that thalidomide inhibits growth of some protozoa and that this was counteracted by nicotinic acid, nicotinamide, and NAD. Six-aminonicotinamide resembled thalidomide in inhibiting growth and again this was prevented by nicotinic acid. Thalidomide in humans, as well as being teratogenic, produced polyneuritis and glossitis. Since nicotinic acid antagonists (antimetabolites) produced teratogenic changes, one might expect similar changes to occur when nicotinic acid is lacking as in pellagra. Fratta et al. (1964) reported that, in rats made pellagrin by vitamin B3-deficient diets, there was a high incidence of fetal death and resorption of embryos.

Hoffer and Osmond (1966) suggested that schizophrenia was an NAD-deficiency

disease. If true, it would not be surprising that schizophrenic women would give birth to more than the average number of congenitally abnormal children. One would have to postulate a differential effect of NAD deficiency on male embryos. This could be tested by examining the ratio of boys to girls in women who have pellagra, it is thus possible to partially account for the peculiar effect of schizophrenia on their offspring by assuming the NAD deficiency which is responsible for the schizophrenia. It may also be responsible for the schizophrenic effect on congenital abnormalities and perhaps on sex ratio.

Greengard et al (1966) found that adrenocortical steroids prevented and brought about remission in rats and dogs of nicotinamide-deficiency disorders. In rats, these hormones prevented fetal death and resorption common in pellagrous rats. According to Greengard et al. and Zak (1968) the steroid hormones would act by increasing availability of tryptophan for synthesis of NAD. Perhaps the female fetus is able to produce more corticosteroid hormones and therefore is better able to protect itself against the teratogenic effect of NAD deficiency.

If NAD deficiency is the main reason in producing increased congenital abnormalities and changes in sex ratio, then these phenomena should not be unique for schizophrenia. In any situation where populations suffer extensive malnutrition one would expect an increase in female births. Therefore, the following quotation from Brillat-Savarin (1960) is most interesting.

"Upon this physiological question I shall say no more; but I must not omit to mention an observation of my own, which can easily be verified.

"Some years ago now, I went to see a country house on the outskirts of Paris, situated to be more exact, in a village on the banks of the Seine, facing the island of Saint-Denis, and mainly consisting of eight fishermen's huts. I was struck by the number of children whom I saw playing there by the roadside.

"I expressed my surprise to the boatman who ferried me across the river.

"Sir,' was his reply, 'there are only eight

families of us, and we have fifty-three children, forty-nine of them girls and but four boys; of those four one is mine; see, there he is.' So saying, he stood up with an air of triumph, and showed me a little monkey five or six years old, sitting in the bows of the boat and enjoying a feast of raw crayfish. The name of that little village is _____

"From this observation, which goes back more than ten years and from others which I cannot so easily describe, I have come to believe that the effect of ichthyophagy upon the sexes is stimulating, but not attended by the most substantial results; and my opinion is borne out by the fact that quite recently Doctor Baily proved, by a series of observations extended over nearly a century, that whenever the annual census of births contains a much larger number of girls than boys, the superabundance of females has invariably been due to debilitating circumstances; and in all probability this is the origin of the jokes which have from time immemorial been made at the expense of the husband whose wife gives birth to a daughter."

What is very interesting is that, in those times, when mankind was uncontaminated by modern sanitation, public health, and preventive medicine, it was possible to recognize a phenomenon of this kind.

The increased birth of girls would have a remarkable effect on rebuilding a population decimated by nutritional catastrophes.

A BIOCHEMICAL HYPOTHESIS WHICH MAY PROVIDE A MECHANISM FOR GENETIC TRANSMISSION OF SCHIZOPHRENIA

There are no biochemical tests specific for schizophrenia nor will there be until there is general agreement that a test which is positive in the majority of schizophrenics shall be used as the independent diagnostic variable. This kind of problem in diagnosis is not unique for schizophrenia.

Every disease which today is diagnosed by a laboratory test had to go through a similar

change in definition. Serological tests are specific because we say they shall be. In other words, we have all agreed that a positive serological test will be sufficient to establish the diagnosis. When this happens for schizophrenia, e.g., when test A positive by agreement indicates schizophrenia, even if present in clinical non-schizophrenia, that person will be diagnosed schizophrenic. It is, therefore, very difficult to claim specificity from an etiological position, and critics of any biological theory will be able forever to deny specificity.

It may be simpler to develop a hypothesis based upon biochemical therapy, especially if several chemotherapies can be shown to operate upon a biochemical mechanism known to be active in the body. I am convinced that vitamin B3, i.e., either nicotinic acid (niacin) or nicotinamide (niacinamide) alone or in combination with the tranquilizer phenothiazines, provide the most specific therapy for schizophrenia so far developed.

Hoffer et al.(1957) was the first to show that vitamin B3 in megadoses of 3 grams per day or more markedly improved the recovery rate when combined with ECT or standard chemotherapy. But before that, it had been used in doses of 2 grams per day or less for organic psychosis. Sydenstricker and Cleckley (1941) and Cleckley et al. (1939) reported recoveries when nicotinic acid was given to cases of stupor, lethargy, and what they termed atypical states. Some of their patients had been diagnosed schizophrenic, but when they recovered on nicotinic acid they were promptly rediagnosed as pellagra psychoses. This, of course, made it certain that no schizophrenic could be said to be treated successfully with nicotinic acid. The chronic schizophrenics who presumably did not recover were still labelled schizophrenic. They require doses up to 30 grams per day for many years combined with tranquilizers. Other organic psychoses which responded were senile psychosis (Gregory, 1952), acute brain syndrome (Martz, 1965), organic con-fusional states (Lehmann, 1944; Hoffer, 1965) and delirium tremens (Gould, 1953, 1954, 1958; Armstrong and Gould, 1955).

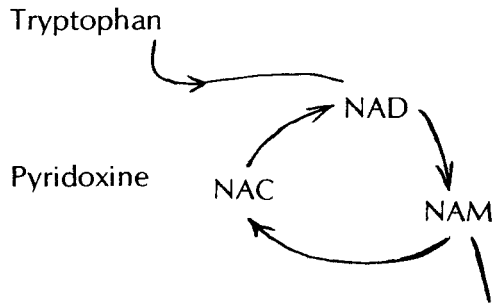
Wolberg et al.(1964) used a nicotinamide derivative, nicotinamide adenylate, and found significant improvement in a series of elderly confused subjects. Washburne (1950), Sherrill (1950), and Thompson and Proctor (1953) used nicotinic acid with good results for depressed patients. It has also been used as an antidote against LSD psychoses in man (Agnew and Hoffer, 1955,

who reported it modified the psychoses). Apparently, some black market LSD is absorbed on nicotinic acid tablets and is sold as a product which yields a superior high. Nicotinic acid dampens down the perceptual component of LSD and reduces anxiety and depression so it could convert bad trips into good ones. It also antagonized the effect of LSD in dogs. Ivanova et al. (1964) had prevented the increase in oxidation of adrenalin in whole blood usually caused by LSD. According to Kanig (1966), nicotinamide antagonized the action of harmine and mescaline in rats and nicotinic acid antagonized the effect of mescal in in rats.

The treatment of schizophrenia with vitamin B3 in megadoses has been developed by five double-blind controlled studies plus a large number of clinical studies in several psychiatric centers. The references in alphabetical order are Ananth, Ban, Lehmann, and Bennett (1970), a double-blind study; Chinaglia (1965), Cott (1967, 1969), Denson (1962), a double-blind study; Foy (1970) Green (1969, 1970), Hawkins (1968, 1969), Hawkins et al. (1970), Herjanic et al. (1967), a double-blind study; Hoffer (1962), reference to two double-blind studies with the first run in 1952 — 53; also Hoffer (1963, 1966, 1966a, 1966b, 1966c, 1967, 1967a, 1967b, 1969, 1970a); Hoffer and Osmond (1960, 1962, 1963, 1963a, 1964, 1966, 1967); Hoffer et al.,(1957); Kowalson (1967); Maslowski (1967); Meiers (1967); Newbold (1970); Osmond (1967); Osmond and Hoffer (1962, 1967); Rimland (1973); Robie (1967); Szatmari et al. (1955); Ward (1967); Zelinskii (1956).

Nicotinamide adenine dinucleotide (NAD),

the coenzyme of vitamin B3, was found effective in treatment of acute and chronic non-institutionalized schizophrenics by Hoffer and Osmond (1967). Kline



et al. (1967) using deteriorated inadequately prepared NAD on a group of chronic deteriorated institutionalized schizophrenics, found no effect. Gallant et al. (1966), using better NAD, also found no effect on equally chronic institutionalized cases. There is a remarkable variability of commercial NAD (McComb and Gay, 1968), and some of the discrepancy may be due to a lack of stable reliable preparation.

At a recent meeting of the American Schizophrenia Foundation, the Committee on Therapy, 1956, reviewed nearly 9,000 cases treated since 1952. All the studies were corroborative. So far, no studies have been published where it has been found that megadose B3 therapy did not yield the same results as described by the authors listed above.

A substantial amount of data has accumulated which shows that the pyridine nucleotide cycle is involved in the genesis of schizophrenia. Gholson (1966) showed that this cycle consists of the following series of reactions.

N Methyl NAM

We need only assume that there is a defect in the turnover of NAD levels which is lowered. It would follow that any substance which increases NAD synthesis or activity will be therapeutic, and any substance which decreases NAD synthesis will be hallucinogenic or aggravate schizophrenics or make them worse. Fortunately, their effect upon NAD

levels is known.

Substances Which Influence NAD Levels

A. By effect on concentration of precursors, e.g., nicotinic acid and nicotinamide. Preiss and Handler (1957) found that nicotinic acid increased NAD levels in red blood cells. Nicotinamide does the same (Hayaishi, 1966). Many investigators have studied the effect of these precursors on NAD levels. Ijichi et al. (1966) found that in small doses nicotinic acid is a better precursor of NAD than nicotinamide but in large doses nicotinamide is better. Primarily nicotinamide served as a precursor to NAD for a prolonged period of time.

Tryptophan may be the most important precursor of NAD in most people. Pellagra which produces a psychosis often indistinguishable from schizophrenia is commonly found low in tryptophan, low in absorbable nicotinic acid or nicotinamide, and high in leucine. There is some evidence that the deficiency in tryptophan is responsible for the skin and gastrointestinal changes of pellagra. I view schizophrenia as a pure dependency state (a relative deficiency state) of vitamin B3 while pellagra is a multiple-deficiency state. It is likely some of the factors which perpetuated chronic schizophrenia in mental hospitals was the malnutrition and decreased protein intake patients suffered some years ago. Faurbye (1968) found that decreasing the intake of tryptophan in schizophrenics provoked a flare-up in hallucinations and delusions.

B. Enzymes which effect conversion of substrates into NAD. Of these the best known is Pyridoxine or vitamin B6 (Rosenberg, 1969). B6-dependency diseases include infantile convulsions, cystathioninuria, xanthurine aciduria and homocystinuria. Because it catalyzes conversion of tryptophan to NAD, a deficiency of B6 can also produce pellagra. Rosenberg (1969) defines a vitamin-dependency disease as a genetic disturbance that leads to specific biochemical abnormalities affecting only one reaction

catalyzed by the vitamin and that responds only to pharmacologic amounts (megadoses).

C. Substances which influence excretion of pyridine molecules. Any substance which increases excretion of pyridine molecules will decrease formation of NAD and should aggravate schizophrenia.

I. By increasing formation of N-methylnicotinamide. This substance can no longer participate in the pyridine nucleotide cycle and is excreted (Sebrell and Harris, 1954). In schizophrenic blood in vitro nicotinamide is methylated much more rapidly to N-methylnicotinamide than in normal blood (Buscaino et al., 1963; Buscaino et al., 1966; and Centili and Borghisi, 1968). There are, therefore, enzymes or activators of methylferase in schizophrenic blood (or lack of an inhibitor).

2. By decreasing formation of N-methylnicotinamide. Burton (1960), Burton et al. (1958), Burton et al. (1960), Burton and Salvador (1962), Burton et al. (1962), Green-gard et al. (1967), Creengard and Quinn (1962), Creengard (1966), Salvador and Burton (1965), Salvador et al. (1959), in a series of studies have shown that tranquilizer drugs like chlorpromazine, promazine, trifluoperazine and reserpine retard decrease of elevated NAD levels after administration of nicotinamide, whereas nontranquilizer phenothiazines and substances like ethanol, phenobarbital, meprobamate have no effect. Substances which were not sedatives had no effect. The effect of tranquilizers was dose related. These authors suggested that nicotinamide methylferase was inhibited, thus decreasing formation of N-methylnicotinamide.

In rats, hypophysectomy increases one-half life of nicotinamide partly due to decreased excretion of nicotinamide and of N-methylnicotinamide (Creengard et al. 1967). Greengard et al. (1966) found that adrenocortical steroids prevented the effects of nicotinamide deficiency in rats and dogs. They prevented the decrease in NAD levels due to diets deficient in nicotinamide. They also protected the animals against the toxic effect of the vitamin B3 antimetabolite, 6-aminonicotinamide. They

suggested that adrenocorticoid hormones stabilized NAD levels in tissues both preventing a decrease in pellagrous animals and preventing an increase in hypophysectomized animals.

Woolley (1958) found that nicotinamide alone was a tranquilizer for mice. Perhaps it acts by elevating NAD levels.

3. By increasing excretion of N-methylnicotinamide.

Copalan (1969), Gopalan and Srikantia (1960) have examined the relationship of vitamin B3 metabolism to pellegra. Pellegra, under control in North America, is still a problem in many parts of the world. The psychosis pellegra is often indistinguishable from schizophrenia when clinical criteria only are used. Gopalan (1969) reports that, in Hyderabad, 8-10 percent of admissions to mental hospitals during certain times of the year are pellegra.

Leucine precipitated psychotic changes in pellagrins and increased the excretion of N-methylnicotinamide. Subjects were given 10 grams of leucine per day and increased excretion of quinolinic acid, a precursor of NAD. Isoleucine counteracted these effects. Leucine also impaired synthesis of nicotinamide nucleotides. Erythrocytes contain nicotinamide mononucleotide (NMN), NAD, and NADH. In pellegra NMN was elevated 20 percent but NAD and NADH were lowered. In controls, only 2¹/₂ percent is present as NMN.

Leucine, 20 - 30 grams per day, produced a striking deterioration in mental condition in pellagrins after seven days. According to Sebrell and Harris (1954) testosterone decreased urinary excretion of N-methylnicotinamide. Maayan and Rosenberg (1968) found that 6-N propylthiouracil greatly increased NAD and NADH in the thyroid gland. On the other hand, alcohol increased the excretion of N-methylnicotinamide.

D. NAD Levels.

In increasing levels - administration of NAD ought to increase cellular levels. Other substances which affect levels (excluding the direct precursors already discussed) are d-amphetamine 10 mg per kg which decreased brain NAD levels by 20 percent. Chlorpromazine had no significant effect, but an inspection of data of Lewis and Pollock (1965) shows that highest mean brain NAD levels in rat brain occurred with 30 mg per kg of chlorpromazine.

According to Appelt et al. (1968), mescaline 100 mg per kg given to mice decreased the brain increase in NAD following intracerebral injection of NAD.

Ethionine is an antimetabolite of methionine which is required for transmethyltion reaction. Ethionine lowers rat liver NAD and NADH (Clark and Pinder, 1966 ; Slater and Sawyer,) probably by inhibiting hepatic ATP synthesis (Palma-Carlos et al. 1966). It also produced porphyria in rats.

Ethionine has not been given to patients. From its two effects (a) in decreasing NAD synthesis which should make schizophrenics worse; (b) as an antimetabolite of methionine which should improve them, it is not possible to predict what would happen. It could be tested in pellagrous animals. Large doses of methionine have made a few subjects more psychotic (Park et al. 1965).

Methionine sulfoximine, another antimetabolite of methionine, generally makes normal subjects psychotic which suggests that ethionine ought to do the same. The production of experimental porphyria in animals would tend to support this view since porphyria in humans is associated with psychotic changes. Perhaps in normal subjects, a decrease in NAD levels is the primary change. However, schizophrenics were temporarily benefitted by methionine sulfoximine suggesting that reduction in transmethyltion was beneficial by reducing excretion of N-methylnicotinamide. But, in chronic trials (after 30 days), signs of organic mental disturbances appeared in schizophrenics.

Ethionine would decrease NAD synthesis and decrease methylation of nicotinamide. The net result on NAD levels is unpredictable. One would suspect that there would be a lowering of NAD in humans and thus a worsening of the clinical picture in the long run even though there might be a transient improvement.

METHODS OF ELEVATING NAD LEVELS AND RESULTS

1. Providing more substrate. Tryptophan, nicotinic

acid, and nicotinamide in megavitamin doses are all therapeutic.

2. Increasing conversion of tryptophan to NAD by giving Pyridoxine (vitamin B6) is therapeutic for infantile convulsions and some forms of retardation.

3. Phenothiazine tranquilizers which decrease formation of N-methylnicotinamide are the mainstay of the chemotherapy of schizophrenia. Reserpine is less effective but would be used if the more efficient tranquilizer had remained unknown. It also elevates NAD levels.

It will not be possible to use hypophysec-tomy as a therapy, but adrenocortical hormones may be helpful when combined with vitamin B3.

WHERE TO LOOK FOR THE GENETIC DEFECT

Pauling (1968) has shown how it can be advantageous to become more dependent upon external sources of essential nutrients such as vitamins. For example, very few species, excluding man, require external sources of ascorbic acid. The chemical enzymes essential to synthesize ascorbic acid have been dropped from human cells. If, therefore, inadequate levels of ascorbic acid are present in the diet, scurvy will be the result. The minimum level required to prevent scurvy will vary from person to person as it will from the optimum level.

Pauling has shown that there are additional biochemical advantages as ascorbic acid levels are increased much above the usual vitamin levels. In evolutionary terms,

the advantage in not having to make ascorbic acid, provided it is present in one's diet, is that biochemical machinery freed from this task can be diverted into other more essential processes.

The concept of vitamin-dependency disease, which has recently developed, suggests that the process of dropping enzymes and becoming totally dependent upon external sources may be incomplete in some animal species. A vitamin-deficiency disease appears in people whose needs for the vitamin are average, but whose intake is much below. But a much smaller number of the population has needs much greater than average and for these people average nutritional doses are inadequate. This is a dependency condition. About a dozen have been described. This means only that the optimal need for these nutrients varies over a much greater range than has been suspected, perhaps a hundred or a thousand-fold. It seems to be a skewed curve with most people having needs which cluster about the usual mean while a smaller number, with much greater needs, appear far from the mean. This latter smaller group will be the vitamin-dependent group.

Nicotinamide adenine dinucleotide (NAD) is made from two sources. It is made from tryptophan, an essential amino acid, and from vitamin B3 in food. The vitamin B3 can be present as nicotinic acid, nicotinamide, or as mono- or dinucleotides. Tryptophan is found in protein in much greater quantities than is B3 in foodstuff, but only a small proportion is converted into B3. It requires about 60 mg of vitamin B3. This estimate may be totally erroneous for certain groups of people. It might be advantageous if NAD could be made entirely from vitamin B3, and the enzymes involved in making it from tryptophan were no longer needed. If this did occur in some people, they would require much larger quantities of vitamin B3 from dietary sources. This could explain dependency conditions.

I suggest that in people who develop schizophrenia, this process has gone further than in most people, i.e., they are less able to make NAD from tryptophan and are more heavily dependent upon dietary NAD. If we are to discover where biochemical geneticists are to look, I suggest that this is a promising area. Using tagged tryptophan, one could discover how much is converted into NAD. According to this suggestion, this reaction will be less active on vitamin B3-dependent subjects. They can readily be located by testing schizophrenics.

Animal experiments have shown that long-continued deprivation of vitamin B3 converts them

from a deficiency into a dependency state. When the animals were maintained on vitamin B3-deficient diets for a short time, they quickly became normal. However, if they were deprived for a long time, they no longer became normal with the same small vitamin doses but, thereafter, required megadoses to remain well. This suggests that enzymes, dependent upon NAD, somehow become permanently impaired and much larger quantities have to be available to the cell before these enzymes function efficiently again.

This is also the case with schizophrenia where it has been demonstrated that very early cases recover and remain well on low megadoses while chronic cases may require doses up to 10 times as great. It is likely that hyperkinetic children who have been shown by Green (1970) and Cott (1969) to be variants of pellagra respond very quickly to B3 if detected and treated early. Dr. Green, a general practitioner, sees these cases very early in its development. Most cases were well in one month. But by the time they are referred to Orthomolecular psychiatrists they have been ill many years and require many months and years of intensive therapy.

I have recently, (Hoffer, 1970), reminded psychiatrists of the remarkable similarity between pellagra and schizophrenia. This was well-known to psychiatrists alive during the pellagra pandemics of the early 20th century. What our geneticist colleagues must do is to

investigate why some people require much larger quantities of B3, how this need is transmitted, and how it can be detected so that early treatment and prevention can be begun.

**THERAPEUTIC TRIALS OF VITAMIN B3
WITH NO ATTEMPT TO REPRODUCE THE
MEGAVITAMIN B3 OR
ORTHOMOLECULAR APPROACH**

A small number of studies have been reported where vitamin B3 was used as one component of the therapeutic program. No attempt was made to follow the total treatment program which has been given in detail many times and which has been followed by all the Orthomolecular physicians who have obtained similar good recovery rates. I cannot understand why there has been no attempt by any research group or University Department outside of Saskatchewan to repeat the entire program.

Either this is due to the well-known conservatism of psychiatric departments who consider themselves part of the psychiatric paradigm and must defend it, or to the fact that investigators are not prepared to do their homework by reading the literature carefully or by personally inspecting the patients and studies of psychiatrists who are able to use the program effectively. Or it may be due to a reluctance to use ECT again, having given it up in favor of tranquilizers. Whatever the reason, there is no denying the fact that so far no attempt has been made to repeat our work surely one of the necessary elements of any corroborative study.

It is necessary to refer to these studies and show where they failed to reproduce the program so that others who wish to enter this field will not make the same error.

The Orthomolecular program depends upon the following variables: (1) use of optimum dose of vitamin B3; (2) use of adequate time which ranges up to seven years; (3) other vitamins; (4) the use of ECT once or more often; (5) the use of the medical model; (6) the use of any one or combination of tranquilizers, antidepressants and other psychoactive

drugs each in their optimum dose. Authors who did not use adequate doses include Ban and Lehmann (1970), Greenbaum (1970), O'Reilly (1955), and Ramsay et al. (1970). In addition, these authors used a fixed, rather brief trial, did not use other adjunctive vitamins, and did not use ECT. Rapp (1968) is a special case because he used Roniacol thinking it was the same as nicotinic acid. It has only very slight vitamin B3 properties. Rapp's paper merely makes a new claim, i.e., that Roniacol does not help alcoholics, but no one had ever claimed it did.

So far every physician who has used the Orthomolecular megavitamin B3 approach has reported equally high recovery rates. Every failure has been due to a failure in methodology.

REFERENCES

- ACNEW, N., and HOFFER, A.: Nicotinic acid modified lysergic acid diethylamide psychosis. *J. Ment. Se.* 101: 12, 1955.
- ANANTH, J. V., BAN, T. A., LEHMANN, H. E., and BENNETT, J.: Nicotinic acid in the prevention and treatment of methionine induced exacerbation of Psychopathology in schizophrenics. *Canad. Psychiat. Ass. J.* 15: 15, 1970.
- APPELT, C. D., WALKER, N. O., and BROWN, R. C.: Effect of mescaline on nicotinamide adenine de-nucleotide synthesis in central nervous system. *J. Pharmaceutical Sciences* 57: 527,1968.
- ARMSTRONG, R. W., and GOULD, J.: The nature and treatment of delirium tremens and allied conditions. *J. Ment. Se.* 101:70, 1955.
- BAN, T. A. and LEHMANN, H. E.: Nicotinic acid in the treatment of schizophrenics. Summary statement — Progress Report I, Canadian Mental Health Association collaborative study. *Canad. Psychiat. Ass. J.* 15: 499, 1970.
- BENDER, L.: Childhood schizophrenia. *Amer. J. Ortho-psychiat.* 26: 499,1955.
- BENDER, L. and HELME, W. H.: A quantitative test of theory and diagnostic indicators of childhood schizophrenia. *Archives Neurology and Psychiat.* 70: 413, 1953.
- BEVERIDGE, W. I. B.: *The Art of Scientific Investigation.* New York, New York: W. W. Norton and Co., 1950.
- BLOCK, J.: Parents of schizophrenic, neurotic, asthmatic and congenitally ill children. *Archives Gen. Psychiat.* 20: 659,1969.
- BRILLAT-SAVARIN, J. A.: *The Physiology of Taste.* New York: Dover Books, 1960.
- BURRELL, R. H., AND OSMOND, H.: Identical twins: an economy in clinical research. *The Lancet* 2: 291, 1959.

- BURTON, R. M.: Alteration of tissue pyridine nucleotide levels and the central nervous system. Inhibition of the Nervous System and Gamma Amino Butyric Acid. E. Roberts Ed.: 249. New York: Pergamon Press, 1968.
- BURTON, R. M., KAPLAN, N. O., GOLDIN, A., LEITEN-BERC, M., HUMPHREYS, S. R., and SODD, M. A.: Effect of reserpine and promazine on diphosphopyr-dine nucleotide synthesis in the liver. *Science* 127: 30, 1958.
- BURTON, R. M., KAPLAN, N. O., GOLDIN, A., LEITEN-BERG, M., and HUMPHREYS, S. R.: Interaction of nicotinamide with reserpine and chlorpromazine III. Some effects on the diphosphopyridine nucleotide content in the liver. *Arch. Int. Pharmacodyn* 128: 260, 1960.
- BURTON, R. M., and SALVADOR, R.: The effect of chlorpromazine on nicotinamide methylferase: an example of drug enzyme interaction at the molecular level. *Ann. N. Y. Acad. Sciences* 96: 353, 1962.
- BURTON, R. M., SALVADOR, A., GOLDIN, A., and HUMPHREYS, S. R.: Interaction of nicotinamide with reserpine and chlorpromazine II. Some effects on the central nervous system of the mouse. *Arch. Intern. Pharmacodyn* 128: 253, 1960.
- BURTON, R. M., SALVADOR, R., SMITH, K., and HOWARD, R. E.: The effect of chlorpromazine, nicotinamide, and nicotinic acid on pyridine nucleotide levels in human blood. *Ann. N. Y. Acad. Sciences* 96: 185, 1962.
- BUSCAINO, G. A., STEFANACHI, L., SALLUSTO, L., SPADETTA, V., and COLUCCI, F.: Metilazione della nicotinamide negli schizofrenici. *Il Lavoro Neuropsi-chiatrico*, 33: 1963.
- BUSCAINO, G. A., SPADETTA, V., and CARELLA, A.: Possible applicazione del test di metilazione in vitro della nicotinamide alia diagnosi biochimica della schizofrenia. *Acta Neurologica* 21: 1, 1966.
- CAPLAN, A. I., ZWILLING, E., and KAPLAN, N. O.: 3-acetylpyridine: Effects in vitro related to teratogenic activity in chicken embryos. *Science* 160: 1009, 1968.
- CARTER, M.: A general practice investigation into possible biological advantages among schizophrenic relatives. *Pers. Comm.*: 1968.
- CARTER, M., and WATTS, C. A. H.: Possible biological advantages among schizophrenics' relatives. *Brit. J. Psychiatry* 118, 453, 1971.
- CHAMBERS, H. W., and CASIDA, J. E.: Protective activity of nicotinic acid derivatives and their 1-allsyl-2 and 1-allsyl-6-pyridines against selected neurotoxic agents. *Toxicology and Applied Pharmacology* 10: 105, 1967.
- CHINAGLIA, L.: Sul trattamento della schizofrenia con amide nicotinic. *Folia Psychiatrica* 8: 123, 1965.
- CLARK, J. B., and PINDER, S.: Control of nicotinamide adenine denucleotide phosphate synthesis in the livers of rats treated with ethionine. *Nature* 210: 631, 1966.
- CLECKLEY, H. M., SYDENSTRICKER, V. P., and CEESLIN, L. E.: Nicotinic acid in the treatment of atypical psychotic states. *JAMA*. 112:2107, 1939.
- COTT, A. A.: Treatment of ambulant schizophrenics with vitamin B-3 and relative hypoglycemic diet. *J. Schizophrenia* 1: 189, 1967.
- COTT, A. A.: Treatment of schizophrenic children. *J. Schizophrenia* 1: 44, 1969.
- COTT, A. A.: The parenteral use of vitamins in the treatment of schizophrenia. *J. Schizophrenia* 2: 177, 1970.
- DENSON, R.: Nicotinamide in the treatment of schizophrenia. *Dis. Nerv. System* 23: 167, 1962.
- EL-MELICI, A. M., and OSMOND, H.: *EWI, Manual for the clinical use of the Experiential World Inventory*. New York: Mens Sana Publishing Co., 1970.
- ERLENMEYER-KIMLINC, L.: Mortality rates in the offspring of schizophrenic parents and a physiological advantage hypothesis' *Nature* 220: 798, 1968.
- ERLENMEYER-KIMLINC, L., RAINER, J. D., and KALLMANN, F. J.: *Psychopathology of Schizophrenia*. New York: Grune and Stratton, 1966.
- FAURBYE, A.: Role of amines in etiology of schizophrenia. *Comp. Psychiat* 9: 155, 1968.
- FISH, B.: The detection of schizophrenia in infancy. *J. Nervous and Mental Disease* 125: 1, 1957.
- FISH, B., and ALPERT, M.: Abnormal states of consciousness and muscle tone in infants bom to schizophrenic mothers. *Amer. J. Psychiat*. 119: 439, 1962.
- FOY, J. G.: *Gone is Shadow's Child*. Watchung, New Jersey: Watchung Book Sales, 1970.
- FRANK, O., BAKER, H., ZIFFER, H., AARONSON, S., HUTNER, S. H., and LEEVY, C. M.: Metabolic deficiencies in protozoa induced by thalidomide. *Science* 139: 110, 1963.
- FRATTA, I., ZAK, S. B., GREENCARD, P., and SIGC, E. B.: Fetal death from nicotinamide deficient diet and its prevention by chlorpromazine and emipramine. *Science* 145: 1429, 1964.
- GALLANT, D. M., BISHOP, M. P., and STEELE, C. A.: DPN (NAD oxidized form): a preliminary evaluation in chronic schizophrenic patients. *Current Therapeutic Research* 8: 542, 1966.
- GENTILI, C., and BORGHISI, E.: Rilievi sue tasso delle transmetilasi en pazienti schizofrenici. *Bollettino della Societa Italiana di Biologia Sperimentale* 43: 14%, 1968.
- GHOLSON, R. K.: The pyridine nucleotide cycle. *Nature* 212: 933, 1966.
- GOPALAN, C.: Possible role for dietary leucine in the pathogenesis of pellagra. *The Lancet* 1: 197, 1969.
- GOPALAN, C. and SRIKANTIA, S. C.: Leucine and pellagra. *Lancet* 1: 954, 1960.
- GOTTESMAN, I. I., and SHIELDS, J.: Schizophrenia in twins: 16 years consecutive admissions to a psychiatric clinic. *Brit. J. Psychiat*. 112: 809, 1966.
- GOULD, J.: Treatment of delirium, psychosis and coma duetodrugs. *The Lancet* 1: 570, 1953.
- GOULD, J.: The use of vitamins in psychiatric practice. *Proc. Royal Soc. Med.* 47: 215, 1954.
- GOULD, J.: The enzymatic basis of certain psychoses. *Recent Progress Psychiatry* 3: 1, 1958.
- GREEN, R. G.: Reading disability. *Canad. Med. Ass. J.* 100: 586, 1969.
- GREEN, R. G.: Protein poor diet means pellagra. *Canad. Family Physician* 16: 88, 1970.
- GREEN, R. G.: Subclinical pellagra: its diagnosis and treatment.

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- J. Schizophrenia 2: 70, 1970.
- GREENBAUM, G. H. C.: An evaluation of niacinamide in the treatment of childhood schizophrenia. *Amer. J. Psychiatry* 127: 129, 1970.
- CREENGARD, P., KALINSKY, H., MANNING, T. J., and ZAK, S.: Prevention and remission by adrenocortical steroids of nicotinamide deficiency disease. II a study of the mechanism. *J. B. C.*: 4216, 1968.
- GREENGARD, P., PETRACK, B., and KALINSKY, H.: Effect of hypophysectomy on pyridine nucleotide metabolism. *J. B. C.*: 242: 152, 1967.
- GREENGARD, P., and QUINN, C. P.: Metabolic effects of tranquilizers and hypophysectomy. *Ann. N. Y. Acad. Sc.* 96: 179, 1962.
- CREENGARD, P., SIGC, E. B., FRATTA, I., and ZAK, S. B.: Prevention and remission by adrenocortical steroids of nicotinamide deficiency disorders and of 6-amino-nicotinamide toxicity in rats and dogs. *J. Pharmacol and Experimental Therapeutics* 154: 624, 1966.
- GREGORY, I.: Nicotinic acid therapy in psychosis of senility. *Amer. J. Psychiat.* 108: 888, 1952.
- HAWKINS, D. R.: Treatment of schizophrenia based on the medical model. *J. Schizophrenia* 2: 3, 1968.
- HAWKINS, D. R.: Treatment of schizophrenia: The psychotherapy versus the chemotherapy controversy. *Newsletter Amer. Schizophrenia Foundation*: 1969.
- HAWKINS, D. R.: *World Medical News, Psychiatric Supplement*: Nov., 1969.
- HAWKINS, D. R., BORTIN, A. W., and RUNYON, R. P.: Orthomolecular Psychiatry: niacin and megavitamin therapy. *Third Int. Congress of Psychosomatic Med., Buenos Aires. Psychosomatics* 11: 517, 1970.
- HAYAISHI, O.: Fifth International Symposium on regulation of enzyme activity and synthesis in mammalian tissues. *Science* 155: 1137, 1966.
- HERJANIC, M., MOSS-HERJANIC, B., and PAUL, W. K.: Treatment of schizophrenia with nicotinic acid. *J. Schizophrenia* 1: 197, 1967.
- HESTON, L. L.: Psychiatric disorders in foster home reared children of schizophrenic mothers. *Brit. J. Psychiat.* 112: 819, 1966.
- HESTON, L. L.: The genetics of schizophrenic and schizoid disease. *Science* 167: 249, 1970.
- HICK, S. P.: Pathologic effects of antimetabolites. *Amer. J. Pathology* 31: 189, 1955.
- HIGGINS, J.: Effects of child rearing by schizophrenic mothers. *J. Psychiat. Research* 4: 153, 1966.
- HOFFER, A.: *Niacin Therapy in Psychiatry*. Springfield, Illinois: C. C. Thomas, 1962.
- HOFFER, A.: Nicotinic acid: an adjunct in the treatment of schizophrenia. *Amer. J. Psychiat.* 120: 171, 1963.
- HOFFER, A.: Treatment of organic psychosis with nicotinic acid. *Dis. Nerv. System* 26: 358, 1965.
- HOFFER, A.: The effect of nicotinic acid on the frequency and duration of rehospitalization of schizophrenic patients: a controlled comparison study. *Int. J. Neuro-psychiat.* 2: 236, 1966.
- HOFFER, A.: *Enzymology of Hallucinogens*. Philadelphia: J.B.Lippincott, 1966a.
- HOFFER, A.: Malvariai and the law. *Psychosomatics* 7: 303, 1966b.
- HOFFER, A.: Use of nicotinic acid and/or nicotinamide in high doses to treat schizophrenia. *Canad. J. Psychiat Nursing* 7: 5, 1966c.
- HOFFER, A.: Five California schizophrenics. *J. Schizophrenia* 1: 209, 1967.
- HOFFER, A.: Biochemistry of nicotinic acid and nicotinamide. *Psychosomatics* 8: 95, 1967a.
- HOFFER, A.: Treatment of schizophrenia with a therapeutic program based upon nicotinic acid as the main variable. *Molecular Basis of Some Aspects of Mental Activity*, p. 435. Ed.: Walaas, O., Vol. 2. New York: Academic Press, 1967b.
- HOFFER, A.: *A Program for Treating Schizophrenia and Other Conditions Using Megavitamin Therapy*. Available from A. Hoffer. Saskatoon: Modern Press, 1967.
- HOFFER, A.: Comparison of xanthine nicotinate and nicotinic acid as treatment for schizophrenia. *J. Schizophrenia* 1: 24, 1969.
- HOFFER, A.: Adverse effects of niacin in emergent psychosis. *J. Amer. Med. Ass.* 207: 1355, 1969.
- HOFFER, A.: *Scientific Committee Reports*. *J. Schizophrenia* 1: 9, 1969.
- HOFFER, A.: Safety, side effects and relative lack of toxicity of nicotinic acid and nicotinamide. *J. Schizophrenia* 1: 78, 1969.
- HOFFER, A.: Pellagra and schizophrenia. *Third IntCongress on Psychosomatic Medicine, Buenos Aires, Jan. 1970. Psychosomatics* 11: 522, 1970.
- HOFFER, A.: Childhood schizophrenia: a case treated with nicotinic acid and nicotinamide. *J. Schizophrenia* 2: 43, 1970a.
- HOFFER, A., and MAHON, M.: The presence of unidentified substances in the urine of psychiatric patients. *J. Neuropsychiatry* 21: 331, 1961.
- HOFFER, A., and OSMOND, H.: *The Chemical Basis of Clinical Psychiatry*. Springfield, Illinois: C. C. Thomas, 1960.
- HOFFER, A., and OSMOND, H.: A card sorting test helpful in making psychiatric diagnosis. *J. Neuropsychiat.* 2: 306, 1961.
- HOFFER, A., and OSMOND, H.: Some schizophrenic recoveries. *Dis. Nerv. Syst.* 23: 204, 1962.
- HOFFER, A., and OSMOND, H.: Scurvy and schizophrenia. *Dis. Nerv. Syst.* 24: 273, 1963.
- HOFFER, A., and OSMOND, H.: Malvaria: a new psychiatric disease. *Acta Psychiat. Scand.* 39: 335, 1963a.
- HOFFER, A., and OSMOND, H.: Treatment of schizophrenia with nicotinic acid. *Acta Psychiat. Scand.* 40: 171, 1964.
- HOFFER, A., and OSMOND, H.: *How to Live with Schizophrenia*. New Hyde Park, New York: University Books, 1966.
- HOFFER, A., and OSMOND, H.: Nicotinamide adenine denucleotide (NAD) as a treatment for schizophrenia. *J. Psychopharmacology* 1: 79, 1966.
- HOFFER, A., and OSMOND, H.: *The Hallucinogens*. New York: Academic Press, 1967.

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- HOFFER, A., OSMOND, H., CALLBECK, M. J., and KAHAN, I.: Treatment of schizophrenia with nicotinic acid and nicotinamide. *J. Clin. Exper. Psychopath.* 18: 131, 1957.
- HUXLEY, J.: Morphism and evolution. *Heredity* 9: 1, 1955.
- HUXLEY, J., MAYR, E., OSMOND, H., and HOFFER, A.: Schizophrenia as a genetic morphism. *Nature* 204: 220, 1964.
- IJICHI, H., ICHIYAMA, A., and HAYAISHI, O.: Studies on the biosynthesis of nicotinamide adenine denucleo-tide. *J. Biol. Chem.* 241: 3701, 1966.
- INOUE, E.: Similarity and dissimilarity of schizophrenia in twins. *Proc. Third World Congress in Psychiatry, Vol. 1, 524. Montreal: McGill University, 1961.*
- IRVINE, D.: Apparently non-indolic Ehrlich-positive substances related to mental illnesses. *J. Neuropsychiat.* 2: 292, 1961.
- IRVINE, D., BAYNE, W., and MIYASHITA, H.: Identification of kryptopyrrole in human urine and its relation to psychosis. *Nature* 224: 811, 1969.
- IVANOVA, R. A., MILSTEIN, G. T., SMIRNOVA, L. B., and FANTCHENKO, N. D.: The influence of nicotinic acid on an experimental psychosis produced by LSD 25. *J. Neuropathology and Psychiat. of C. C. Korsaloff (Moseon)* 64: 1172, 1964.
- JARVIK, L. F.: Congenital malformations attributed to sleeping pill (thalidomide). *Eugenics Quarterly* 9: 95, 1962.
- KALLMANN, F. J.: The genetic theory of schizophrenia. *Amer. J. Psychiat.* 103: 309, 1946.
- KANIG, K.: Tierexperimentelle untersuclungen zur frage der wirkungsweise von niacin und niacinamid bei der therapievon psychosen. *Proc. IV World Cong. Psychiatry, Madrid, Sept., 1966. Excerpta Medica International Congress Series No. 150.*
- KARLSSON, J. L.: The Biologic Basis of Schizophrenia. Springfield, Illinois: C. C. Thomas, 1966.
- KARLSSON, J. L.: Evidence for hereditary transmission of schizophrenia. *J. Schizophrenia* 1: 239, 1967.
- KELM, H., HOFFER, A., and OSMOND, H.: H offer-Osmond Diagnostic Test Manual. Saskatoon: Modern Press, 1967.
- KLINE, N. S., BARCLAY, C. L., COLE, J. O., ESSER, A. H., LEHMANN, H., and WITTENBORN, J. R.: Controlled evaluation of nicotinamide adenine denucleotide. *Brit. J. Psychiat.* 113: 731, 1967.
- KOWALSON, B.: Metabolic dysperception: its diagnosis and management in general practice. *J. Schizophrenia* 1: 200, 1967.
- LANDAUER, W.: *J. Exp. Zool.* 136: 509, 1957.
- LEHMANN, H.: Post traumatic confusional state treated with massive doses of nicotinic acid. *Canad. Med. Ass. J.* 52: 558, 1944.
- LEWIS, J. J., and POLLOCK, D.: Effects of d-amphetamine and chlorpromazine on oxidized (NAD) and reduced (NADH 2) nicotinamide adenine denucleotide levels in rat brain. *Biochem. Pharmacol.* 14: 636, 1965.
- MCCOMB, R. B., and GAY, R. J.: A comparison of reduced NAD preparations from four commercial sources. *Clin. Chem.* 14: 754, 1968.
- MAAYAN, M. L., and ROSENBERG, I. N.: Pyridine nucleotides in the thyroid gland II effect of nicotinamide, nicotinic acid and 2 tryptophane administration. *Endocrinology* 82: 209, 1968.
- MARTZ, D. M.: Acute brain syndrome secondary to niacin deficiency. *Amer. J. Psychiat.* 122: 215, 1965.
- MASLOWSKI, J.: Nicotinic acid in treatment of chronic schizophrenia. *Psychiatria Polska* 1: 307, 1967.
- MEIERS, R. L.: Relative hypoglycemia in schizophrenic reactions. *J. Schizophrenia* 1: 204, 1967.
- MELLOR, C. S.: Finger prints in schizophrenia. *Nature* 213: 939, 1967.
- NEWBOLD, H. L.: How one psychiatrist began using niacin. *Schizophrenia* 2: 150, 1970.
- O'REILLY, P. O.: Nicotinic acid therapy and the chronic schizophrenic. *Dis. Nerv. System* 16: 67, 1955.
- OSMOND, H.: Background to the niacin treatment. *J. Schizophrenia* 1: 125, 1967.
- OSMOND, H., and HOFFER, A.: Massive niacin treatment in schizophrenia. Review of a nine-year study. *Lancet* 1: 316, 1962.
- OSMOND, H., and HOFFER, A.: Schizophrenia and suicide. *J. Schizophrenia* 1: 54, 1967.
- PALMA-CARLOS, A., PALMA-CARLOS, L., GAJDOS-TOROK, M., and CAJDOS, A.: Experimental porphyria induced in rats by ethionine. *Nature* 211: 977, 1966.
- PARK, L. C., BALDESSARINI, R. J., and KETY, S. S.: Methionine effects on chronic schizophrenics. *Arch. Gen. Psychiat.* 12: 346, 1965.
- PAULING, L.: Orthomolecular psychiatry. *Science* 160: 265, 1968.
- PAULING, L.: Orthomolecular somatic and psychiatric medicine. Sonderdruck aus der Zeitschrift *Vitalstoff-Zivilisationskrankheiten*, 1: 1968.
- PAULING, L.: Vitamin therapy: treatment for the mentally ill. *Science* 160: 1181, 1968.
- POLLIN, W., STABENAU, J. R., and TUPIN, J.: Family studies with identical twins discordant for schizophrenia. *Psychiat.* 28: 60, 1965.
- PREISS, J., and HANDLER, P. C.: Synthesis of diphospho-pyridine nucleotide from nicotinic acid by human erythrocytes in vitro. *Amer. Chem Soc. J.* 79: 1514, 1957.
- RAINER, J. D.: Expanding Goals of Genetics in Psychiatry. New York: Grune and Stratton, 1962.
- RAMSAY, R. A., BAN, T. A., LEHMANN, H. E., SAXENA, M. A., and BENNETT, J.: Nicotinic acid as adjuvant therapy in newly admitted schizophrenic patients. *Canad. Med. Ass. j.* 102: 939, 1970.
- RAPP, M. S.: Use and abuse of drugs. *Canad. Med. Ass. J.* 98: 922, 1968.
- RIMLAND, B.: The institute for child behavior research study of high dosage vitamins as a method of treating severely mentally ill children. Conference and annual meeting, National Society for Autistic Children. San Francisco, 1970.
- RIMLAND, B.: High-dosage levels of certain vitamins in the treatment of children with severe mental disorders. *Orthomolecular Psychiatry*. Ed.: Hawkins, David R., and Pauling, Linus. San Francisco: W. H. Freeman and Company, 1973.

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- ROBIE, T. R.: Cyproheptadine: an excellent antidote for niacin induced hyperthermia. *J. Schizophrenia* 1: 133,1967.
- ROGER, J. C, CHAMBERS, H., and CASIDA, J. E.: Nicotinic acid analogues: Effects on response of chick embryos and hens to organophosphate toxicants. *Science* 144: 539,1964.
- ROSENBERG, L. E.: Inherited aminoacidopathies demonstrating vitamin dependency *The New England J. of Medicine* 281: 145, 1969.
- ROSENTHAL, D.: Problems of sampling and diagnosis in the major twin studies of schizophrenia. *Psychiat. Res.* 1: 116,1961.
- ROSENTHAL, D.: The offspring of schizophrenic couples. *J. Psychiat. Res.* 4: 169, 1966.
- ROSENTHAL, D., WENDER, P. H., KETY, S. S., SCHULSINGER, F., WELNER, J., and OSTERGAARD, L.: Schizophrenics Offspring Reared in Adoptive Homes, 377. New York: Pergamon Press, Inc., 1968.
- SALVADOR, R. S., and BURTON, R. M.: Inhibition of the methylation of nicotinamide by chlorpromazine. *Biochem. Pharm.* 14: 1185, 1965.
- SALVADOR, R., BURTON, R. M., KAPLAN, N. O., GOLDIN, A., and LEITENBERG, M.: Effects of reserpine and chlorpromazine on pyridine nucleotide synthesis. 135th Meeting American Chemical Society. Boston, 1959
- SEBRELL, W. H., and HARRIS, R. S.: *The Vitamins*, Vol. 2, 449, New York: Academic Press, 1954.
- SHEARER, M. L, DAVIDSON, R. T., and FINCH, S. M.: The sex ratio of offspring born to state hospitalized schizophrenic women. *J. Psychiat. Res.* 5: 349, 1967.
- SHERRILL, D.: Nicotinic acid in the treatment of certain depressed states. *J. Bowman Gray School Medicine* 8: 137,1950.
- SHIELDS, J., GOTTESMAN, I. I., and SLATER, E.: Kallmann's 1946 schizophrenic twin study in the light of new information. *Acta Psychiatrica Scand.* 43: 385, 1967.
- SLATER, E.: Psychotic and neurotic illnesses in twins. *Med. Res. Council Special Report No. 278.* London, 1953.
- SLATER, T. F., and SAWYER, B. C.: Nicotinamide adenine denucleotides in acute liver injury induced by ethio-nine and a comparison with the effects of salecylate. *B.J.* 101: 24, 1966.
- STONE, I.: Studies of a mammalian enzyme system for producing evolutionary evidence on man. *Amer. J. Phys. Anthrop.* 23: 83, 1965.
- STONE, I.: Hypoascorbemia, the genetic disease causing the human requirement for exogenous ascorbic acid. *Perspectives in Biol, and Med.* 10: 133,1966.
- SYDENSTRICKER, V. P., and CLECKLEY, H. M.: The effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. *Amer. J. Psychiat.* 98: 83, 1941.
- SZATMARI, A., HOFFER, A., and SCHNEIDER, R.: The effect of adrenochrome and niacin on the electroencephalogram of epileptics. *Amer. J. Psychiat.* 111: 603, 1955.
- TAYLOR, M. A.: Sex ratios of newborns: associated with prepartum and postpartum schizophrenia. *Science* 164: 723,1969.
- TAYLOR, M., and LEVINE, R.: The effect of maternal schizophrenia on the sex of offspring. *Soc. Biol. Psychiat.*: May 2,1969,
- TAYLOR, M. A., and LEVINE, R.: Puerperal schizophrenia: a physiological interaction between mother and fetus. *Biological Psychiat.* 1: 97,1969.
- THOMPSON, L. J., and PROCTOR, R. C: Depressive and anxiety reactions treated with nicotinic acid and phenobarbital. *N. Carolina Med. J.* 14: 420, 1953.
- WARD, J. L.: Treatment of neurotics and schizophrenics using clinical and HOD criteria. *J. Schizophrenia* 1: 140, 1967.
- WASHBURNE, A. C: Nicotinic acid in the treatment of certain depressed states: a preliminary report. *Ann. Int. Med.* 52: 261, 1950.
- WENDER, P. H.: The role of genetics in the etiology of the schizophrenias. *Amer. J. Orthopsychiat.* 39: 447, 1969.
- WHITTEN, C. F., PETTIT, M. C., and FISCHOFF, J.: Evidence that growth failure from material deprivation is secondary to underreating. *J. Amer. Med. Ass.* 209: 1675,1969.
- WOLBERG, L. R. RIESSE, B. F., DI CYAN, E. D., and DAIN, H. J.: The "Curtain of Fog" syndrome. *Mind* 2: 75, 1964.
- WOOLLEY, D. W.: Tranquilizing and antiserotonin activity of nicotinamide. *Science* 128: 1277,1958.
- ZELINSKII, S. P.: *Chem. Abstracts* 50:1956.

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Errata

Following are corrections to errors which appeared in ORTHOMOLECULAR PSYCHIATRY, Volume 1, Numbers 2 and 3 of 1972.

On page 126, "A Study of Neurological Organization Procedures and Megavitamin Treatment for Children with Brain Dysfunction", by Stanley Krippner, Ph.D., and Stuart Fischer, the last sentence in column one should have read, "The mean CA for this group was 1-10 with a range of 0-9 to 3-1."

On page 139, in "Glucose Tolerance in Schizophrenia," by Jack L. Ward, M.D., first column, second paragraph, a sentence should have read, "However, the incidence of diabetes (as defined by the glucose-tolerance test figures of 160 mg percent at one hour and 120 mg percent at two hours) in the general population in the United States is put at 2 percent known cases and 1 percent undetected cases."

On pages 143 and 144 in "Pharmacological and Toxic Effects of Kryptopyrrole in Mice," by L. Wetterberg, M.D., Ph.D., the last sentence should have read, "Neuromuscular apparatus impairment developed at a lower dose level than the analgesic effect, since five mice were unable to climb the cylinder in the hot plate test even though they reacted to the heat stimulus by licking their front feet."