MEGAVITAMIN AND ORTHOMOLECULAR THERAPY IN PSYCHIATRY

A Report of the APA Task Force on Vitamin Therapy in Psychiatry

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I. INTRODUCTION

Almost twenty years ago a hypothesis was formulated which attempted to integrate the psychological, biochemical and clinical findings in schizophrenia (1). From this there was derived a mode of treatment for schizophrenia which employed massive doses of vitamin B_3 added to other existing forms of treatment such as electroconvulsive therapy and barbiturates. Over the past twenty years, the research of many workers has yielded new concepts regarding the etiology of schizophrenia with increasing acceptance of a genetic diathesis (2) and a biological defect in schizophrenia although the nature of the defect is still a matter of speculation. Several new testable hypotheses have been offered (3). Simultaneously there has been increasing acceptance of pharmacotherapy with phenothiazines and the butyrophenones as crucial, though perhaps not sufficient, in the treatment of this illness. Emphasis upon insight oriented psychotherapy has diminished (4, 5). The National Institute of Mental Health supports research in schizophrenia at a level of $10 million annually.

In this same time period the originators of the treatment based on massive doses of niacin have also shifted their theoretical position and their form of treatment.

Megavitamin therapy is today a concept and term which is loosely defined. Initially, the term dealt with the use of very large doses of vitamin B_3 (nicotinic acid or nicotinamide) for the treatment of schizophrenia. Later it included the use of nicotinamide adenine dinucleotide (NAD), the co-enzyme derived from vitamin B_3. Over the years it has evolved to include ascorbic acid, pyridoxine (vitamin B_6), folic acid, vitamin B_{12}, and other vitamins, minerals, hormones, diets and drugs. It has also changed its name. The treatment is now called orthomolecular treatment (6).

This treatment has always been added onto existing conventional somatic treatments for schizophrenia. For example, in studies initiated in 1952, before psychotropic drugs were available, vitamin B_3 was initially offered as a valuable adjunct to ECT and the barbiturates, the treatments available for schizophrenia at that time. When psychotropic drugs became available, vitamin B_3 was considered initially as a competitor for these agents with the claim that while it

was slower in action, it was ultimately more effective and less toxic. Today, all of the psychotropic drugs are usually incorporated into the treatment program at the judgment of the physician and ECT is still frequently used, but large doses of additional vitamins and other nutrients are added to whatever other treatments are employed.

The theoretical base for the use of vitamins in "mega" doses has also shifted over the years. Initially, it was hypothesized that vitamin B_3 acted as a methyl group acceptor which reduced the formation of an endogenous psychotogen (adrenochrome and adrenolutin) (7). Today, it is argued that schizophrenia is an incipient form of cerebral pellagra based upon individually idiosyncratic needs for exceptional quantities of the vitamin because of a postulated block between the substrate vitamin B_3 and its synthesis into the coenzyme NAD (8).

Advocates of megavitamin therapy received substantial support in 1968 when so prestigious a figure as Pauling (9) presented a theoretical paper supporting the possibility that some forms of mental illness might be due to vitamin deficiencies occurring even on ordinarily adequate diets. Such deficiencies could be conceivably due to genetically idiosyncratic needs for exceptionally large doses

of vitamins. This concept was called orthomolecular psychiatry. Advocates of megavitamin therapy fully support Pauling's concept, have changed the name of the treatment, and now call their practice orthomolecular psychiatry. This is defined as "the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentration of substances normally present in the human body" (9. p. 265). According to this view, the schizophrenias are a group of illnesses with different biochemical aberrations, so that as each biochemical abnormality is discovered and corrected, an increasing percentage of patients will recover. ". . . clinicians practicing Orthomolecular Psychiatry are using a combination approach which varies from patient to patient depending upon the biochemical peculiarities of the given case and which often includes high doses of niacin or niacinamide, ascorbic acid, pyridoxine, vitamin E, thyroid, vitamin B_{12}, hypoglycemic and cereal free diets, daily physical exercise, lithium, the phenothiazines and also the commonly used tranquilizers and antidepressants." (10, p. 518). ECT is still frequently used (11, 12, 13, 14, 15). Nothing is said in this or similar publications as to how the biochemical peculiarities are elucidated, nor corrected. In a strict sense the term "orthomolecular" is a misnomer. There is nothing orthomolecular about the electroconvulsive therapy or the psychotropic drugs which hospitalized patients and many outpatients receive.

It should be clear from the above that what was initially proposed as a specific vitamin B_3 addition in the treatment of schizophrenia has now become a school of nutritional thought which employs conventional somatic treatments but adds on large doses of single or multiple vitamins often in combination with minerals, hormones, and special diets. This school clearly adheres to an organic and metabolic etiology of schizophrenia and other forms of major mental illness. It vigorously opposes psychogenic etiology or insight oriented psychotherapy. The treatment program has been reported to be useful in the treatment of hyperactive children, childhood autism, alcoholism, adverse reactions to psychotomimetic drugs, arthritis, hyperlipidemia, geriatric problems, and even some forms of neurosis and depression (12, 13, 16, 17, 18).

Results claimed by advocates of megavitamin therapy were initially modest and supported by their own published data. More recently they have tended to become categorical statements which are offered without systematic documentation. Thus, in the recent publication referred to above, Hawkins et al. state: "Since then [1966] we have treated over 2,000 schizophrenic patients utilizing Orthomolecular therapy with increasingly satisfactory results." (10, p. 518). A program for the prevention of schizophrenia has been recommended by Hoffer: "It follows that enrichment of our food with vitamin B_3 will prevent most cases of pellagra or of schizophrenia from becoming manifest. I estimate that one gram per day started early in life will protect most of us" (8, p. 525).

A school of thought and a therapeutic program which promises so much for the prevention and treatment of schizophrenia and other major mental illness has attracted a few advocates from the medical and psychiatric profession and many more from the lay public. Organizations like the American Schizophrenia Association, the Huxley Society and the Association of Orthomolecular Psychiatrists are founded on the principles and practice of this school of thought. The American Schizophrenia Association has established its own journal which has at different times been called the *Journal of the American Schizophrenia Association, Schizophrenia,* and is now called the *Journal of Orthomolecular Psychiatry.* Several popular books have been written for the lay public. Among these are Hoffer and Osmond, *How to Live with Schizophrenia* (New York, 1966); Pfeiffer, Osmond et al., *The Schizophrenias: Yours and Mine* (New York, 1970); and Foy, *Gone is Shadow's Child* (Watchung, N.J., 1970).

Considerable publicity has been obtained in newspapers and magazines. Since megavitamin therapy has not been generally ac-

cepted by the psychiatric and medical professions, in most of the publications the virtues of the megavitamin approach have been lauded by the proponents while the psychiatric profession has been severely criticized for its failure to accept their principles and practice.

Should the theoretical structure of orthomolecular psychiatry and the claims of therapeutic effectiveness be correct, then certainly the psychiatric profession has been guilty of ignoring a highly useful treatment for a seriously crippling group of illnesses. Should the claims supporting megavitamin treatment be incorrect or lacking in substance, the tragic consequences of advocacy of an ineffective treatment follow. For this reason we shall examine carefully and critically the claims, the supporting evidence, the theoretical basis, and the contrary evidence in detail. This is not a simple task because, as stated previously, both the claims and the therapeutic program have shifted substantially over the years. Consequently, when a serious scientific attempt is made to replicate the clinical experiments under the specific conditions for which the original claims were made, one finds that the conditions have changed. Orthomolecular psychiatrists constantly protest that failures to replicate

their results stem from inappropriate selection of patients and from the failure to utilize all of the components of their present program. The latter claim is probably correct because it is virtually impossible to replicate studies in which each patient receives a highly individualized therapeutic program with from one to seven vitamins in huge doses, plus hormones, special diets, other drugs and ECT, which are added or subtracted not on the basis of proved biochemical abnormalities but rather on the basis of the clinicians' individual judgment as to the patient's needs. It is also impossible to replicate studies in which as many as five years of treatment may be needed before results begin to appear.

Over the last fifteen years megavitamin advocates have emphasized vitamin B_3 as the crucial variable in the therapeutic program. It is, therefore, this vitamin which has been most extensively studied in attempts to replicate the work of the proponents of megavitamin therapy. The rigorous double-blind studies with vitamin B_3 or its enzyme conducted by clinical psychiatrists and psychopharmacologists who were not initial advocates of this treatment rationale have failed to confirm the positive results of megavitamin therapy. Arguments that these studies are not relevant because they do not address themselves to the complete therapeutic program as it is employed in 1972 would appear to have little merit because the claims made for the newer procedures are not based upon rigorously controlled

studies and have not been published in careful detail. On the other hand, the careful attempts at replication which have been conducted deal with explicit procedures and published data-based claims of the efficiency of vitamin B_3. If these specific claims are found wanting, the credibility of all present and future claims which are offered is diminished, and it becomes the responsibility of the orthomolecular psychiatrists to submit their procedures and results to the scientific and clinical community in sufficient detail to permit its critical scrutiny.

II. CLAIMS FOR THE EFFECTIVENESS OF THE MEGAVITAMIN RATIONALE

From its inception, proponents of megavitamin therapy have made striking, and often unsupported, claims regarding its efficacy. The unqualified form of so many of these claims has in itself been sufficient to arouse some measure of suspicion on the part of many experienced psychiatrists. Examples:

1. Hoffer (12): "There is no doubt that a major proportion of schizophrenics recover on vitamin B_3. Any psychiatrist who begins with a cohort of 100 acute schizophrenics and follows the orthomolecular approach for a sufficient period of time, say three years, will find that 90% of his patients are well, the rest are improved, none will be worse." (p. 107).

2. Hoffer (19): "All the acute patients given nicotinic acid responded equally well to treatment . . ." (p. 239).

3. *Ibid.*: "This (sic) data and that published before leaves no room for doubt. Nicotinic acid used as described greatly improves the outcome of schizophrenia . . ." (p. 240).

4. Cott (17): "I have seen very few cases of childhood schizophrenia, autism or brain injury in whom seizure activity did not respond to the megavitamins." (p. 98).

5. Hoffer (12): ". . . without exception every psychiatrist who has used the orthomolecular approach as described has become very impressed. They were able to double their recovery rate." (p. 107).

6. "Schizophrenic patients treated with nicotinic acid as described by Hoffer [20] make much better recoveries than when this innocuous vitamin is omitted from the treatment program." (19, p. 240).

7. "Patients on nicotinic acid in all the groups were better off. They had fewer readmissions, fewer days in hospital, fewer patients in hospital on the target follow-up date and did not have any suicides. These results are so strikingly different that no statistical tests are required." (19, p. 239).

8. "The earlier in the course of the illness treatment is begun, the better are the results. Over 90% of all schizophrenics who have been ill less than one year and have not been injured by incarcera-

tion in inadequate mental hospitals should recover and remain well if they take medication regularly. Patients who have become chronic in mental hospitals have a much poorer prognosis. Nevertheless, the results of any therapeutic program are markedly improved by the addition of nicotinic acid" (21).

9. "Every schizophrenic is deprived of a chance for full recovery if nicotinic acid or nicotinamide, or both, are withheld from the program of treatment" (21).

10. Osmond (22), in discussing a proposed four-year NIMH sponsored study on the effects of nicotinic acid at the N.J. State Hospital, said, "Considerable research in Canada and in the United States has been generated to examine the effectiveness of this form of treatment. One such project, the Wittenborn Study (23), involves a double-blind four year experiment which was begun in 1968." In discussing the four-year wait before the results, he further stated, "During those four years at least 200,000 young people will develop schizophrenia in the United States alone. What is their fate, using every treatment known today excluding niacin, likely to be? Between 35%-40% (70-80,000 patients) will recover from their initial illness which may last from some weeks to several years. After this they
2 will not have a recurrence. About 30% (60,000 patients) will have one or more attacks of schizophrenia requiring further treatment in hospital during their lifetime. The 30% remaining another 60,000 patients (sic) will be seriously ill for much of the time. At the end of the four years we would expect about 10% that is, 15 to 20,000 of the original 200,000 patients to be in some kind of psychiatric hospital there (sic) will have been about 105,000 admissions, resulting in some 26,900 years spent in hospital. Because the suicide rate of patients with schizophrenia . . . is about 20 times that of healthy people of the same age, between 750 and 1000 of them will commit suicide during the four years.

"Our findings . . . strongly suggest that if in addition to such other treatment as is deemed necessary, niacin were to be given to these same 200,000 patients in the dosage and manner which we advise, as soon as the illness is recognized, the outcome would be different. Between 75% and 80% (150-160,000 patients) will become well and will stay well; between 3-6,000 patients will be in hospital for about 20,000 admissions, resulting in some 2250 years in hospital. Suicides would be substantially less. Our figures indicate that the suicide rate is (sic) those taking niacin comes much closer to the normal rate. There might be 80 to 100 suicides during the four years. The cost of saving those several hundred lives would be about 10 cents per patient per day, which does not seem excessive."

11. Summarizing his conclusions in 1967, Hoffer (18) states: "1. Early cases of schizophrenia respond better than chronic cases. 2. Longer treatment prevents relapse more effectively than short treatment. The ten-year cure rate is over 75 per cent compared to the control rate of 35 per cent. A ten-year cure is a patient who has been free of schizophrenic symptoms and has not required hospital treatment for the schizophrenia during those ten years. Several patients begin to recover after 5 to 7 years of continuous nicotinic acid therapy. 3. Nicotinic acid is more effective than nicotinamide for chronic schizophrenia. 4. Nicotinic acid potentiates the action of barbiturates, anticonvulsants and tranquilizers. 5. Nicotinic acid is remarkably safe and easy to administer. . . . In over 400 cases in Saskatchewan we have seen no cases of toxicity." (p. 29).

12. "NAD [nicotinamide-adenine-dinucleotide] is therapeutic for schizophrenia more quickly and in lower doses [than nicotinic acid], and some of the responses were as rapid as responses of pellagrins to nicotinic acid; there is a remarkable similarity between pellagra and schizophrenia" (24, p. 92).

13. "The treatment of schizophrenia has been unsatisfactory for centuries and it is little better today than it was . . . in 1830. . . . Tranquilizers have at least two serious disadvantages. They suppress the symptoms in many patients who nevertheless do not recover, and they are often toxic when used in large doses for long periods of time. . . . Many drugs which show less toxicity have already been withdrawn from medical use" (24, p. 79).

It is certainly true that the prevention and treatment of schizophrenia have been—and are—far from what psychiatrists would like them to be. Advocates of the megavitamin rationale have suggested that the resistance on the part of the psychiatric community to the acceptance of their procedures stems from (1) their commitment to a psychogenic etiology for schizophrenia, (2) the absence of any commercial interest in vitamin B_3, (3) a reluctance to accept the concept of schizophrenia as a cofactor deficiency disease. In the lay press and in the *Journal of Schizophrenia* there have been allusions to the fact that at least 6,000 patients have responded favorably to the treatment and that many more thousands of unfortunate patients have been denied the benefits of this treatment.

The arguments advanced by Hoffer and Osmond and their supporters as to why their treatment has largely been ignored by psychiatry probably contain a grain of truth. If, however, they contained the full truth, psychiatry would indeed be in a sorry state, gullible to the seduction of advertisement, pitiful in its naiveté, committed to an ideology, and reprehensible in its prejudice. Surely

another possibility exists. It is that the hypothetical structure on which megavitamin therapy is based has little scientific support, and that legitimate empirical attempts at scientific replication have failed. We submit that these are more proper reasons why this treatment program has not received wide professional acceptance and shall now examine the theoretical structure, the present state of their evidence as well as the data from other current research programs, designed to evaluate their claims.

III. EARLY THEORETICAL RATIONALE AND CLINICAL TRIALS WITH NA AND NAA: CRITICISMS AND ATTEMPTS AT REPLICATION

After W. B. Cannon (25) had published his discovery of the role of adrenal hormones in the adaptation to stress, the notion that abnormal mental states are the result of a faulty metabolic adaptation to overwhelming environmental stimulation was entertained by various psychiatric researchers. Among the first were Osmond and Smythies (26), who formulated the hypothesis that schizophrenia is the outcome of stress-induced anxiety and a failure of metabolism which results in highly toxic mescalin-like ('M') compounds. Harley-Mason (quoted in (26)) suggested that 3,4-dimethoxyphenylethylamine (DMPEA) is the toxic agent responsible for the psychopathological changes and put forward the hypothesis that the production of DMPEA (in the adrenals) is the result of "transmethylation," in which the normal physiological N-methylation of norepinephrine to epinephrine is replaced by the pathological O-methylation of the phenol ring of dopamine. In favor of this hypothesis was the early finding that DMPEA in animal studies induced "experimental catatonia" (27, 28).

An alternative hypothesis proposed by Hoffer suggested that adrenochrome, a psychotoxic oxidation product of epinephrine, was the 'M' substance (7). Its production was thought to be the result of the increased phenolase (oxidase) activity of schizophrenic serum (29, 30). That adrenochrome can be obtained by treating epinephrine with various oxidants (including inorganic) had been demonstrated long before the adrenochrome hypothesis of schizophrenia was formulated (31). The proposed enzymatic formation of adrenochrome *in vivo* in schizophrenia was new.

The first major publication by Hoffer and Osmond specifically claiming the efficacy of nicotinic acid in the clinical treatment of schizophrenia was in 1957 (11). The rationale for their trial of nicotinic acid was approximately as follows. Epinephrine is synthesized *in vivo* from norepinephrine by N-methylation. Epinephrine,

but not norepinephrine, can be oxidized *in vivo* to adrenochrome and adrenolutin. These latter compounds administered to normal subjects produced psychological changes which fall within the range of schizophrenic reactions. Both of these compounds could be formed endogenously by patients with schizophrenia. Nicotinic acid is a strong methyl group accepter. It could, therefore, compete for methyl groups and thus prevent the conversion of norepinephrine to epinephrine. Diminution of epinephrine would diminish the quantities of adrenochrome and adrenolutin formed and would be helpful in schizophrenia. This rationale remains unproved. Not only is there no evidence for adrenochrome formation *in vivo*, but the psychotomimetic properties of adrenochrome have also not been replicated.

In their first experiments, started in 1952, they compared in a double-blind study patients given nicotinic acid and nicotinamide at doses of 3.0 grams/day for 30 days with other treatments available at that time. The major tranquilizers were not yet available. ECT and sedation were given to all patients as needed, but insulin shock and autonomic drugs were avoided. Assessment of results during the hospitalization was by clinical evaluation of symptom intensity. At the end of the 33 days the patients were discharged home or rarely to a mental hospital. Follow-ups after discharge from the hospital were by contact every three months with patients and relatives to assess adjustment to the community, job, and family. The follow-ups were made by social workers who did not know the treatment given, and occasionally by letters and questionnaires. Follow-up varied from about a year to somewhat more than three years. Readmission to hospital was used as a criterion of failure of treatment. The results showed only small degrees of improvement on the vitamin over placebo during the hospitalization but a decreased relapse rate in the first four years in the nicotinic acid group related to use of drug either in hospital or upon follow-up. Of the 74 patients who received drug in hospital, only 13 took nicotinic acid after discharge. Relapse rates for the two groups became the same after four years. In this study, then, only thirty days of hospital treatment with nicotinic acid compared with placebo, resulted in significant improvement at home or in the community and fewer relapses over the next four years.

A second double-blind study took place beginning in June of 1953 (20, 32). During a period of five years, a total of 82 patients were studied, 43 of whom received placebo and 39 of whom received nicotinic acid. In this study, the nicotinic acid group had significant improvement in the hospital, but little difference in the relapse rate. The only patients who had a significant improvement with nicotinic

acid continued after discharge from the hospital were seven acutely ill females with a mean age of 23 years. Hoffer points out that acute schizophrenics seem to respond more favorably to nicotinic acid in the community. This group also received ECT, barbiturates and psychotherapy but no insulin or tranquilizers.

In March 1962, Denson (15) reported a double-blind study of 36 acute and chronic hospitalized schizophrenic patients who received nicotinamide as a part of their treatment regime. The patients studied were all male and represented about ⅓ of the total number of male schizophrenic patients who entered the hospital during the period of selection. Only those patients who required ECT were chosen. Most of the patients received ataractic drugs before, during and after the five-week period of treatment with nicotinamide or placebo. The only criterion of improvement was duration of stay in hospital. (Denson showed that patients who received nicotinamide in the hospital were in hospital 71 fewer days on the average.) It is of interest that only two of the patients in the nicotinamide group had more than two admissions in contrast to seven in the placebo group.

Positive claims for the efficacy of nicotinic acid have been made by other workers following open clinical trials (10, 15, 16, 17, 33, 34, 35, 36, 37, 38, 39, 40).

In 1963 (14) Hoffer and Osmond published a ten year follow-up evaluation of patients included in their initial studies. Using one or more hospital readmissions as their criterion for therapeutic success, the authors state: "No statistical finesse is required to see that the nicotinic acid patients fared much better than the others. Twelve out of sixteen or 75 per cent of the nicotinic acid group did not require readmissions for ten years, i.e. there has been a 75 per cent ten year cure rate. Ten out of 27 or 36 per cent of the comparison group were 10 year cures. These results are much like those reported in other nicotinic acid papers. . . ." (p. 176). In the concluding remarks in this paper, the authors state: "Two-thirds of those who develop schizophrenia are more or less crippled by it and return to hospital for periods ranging from a few weeks to several years. Our studies suggest that at least half of the crippled two-thirds will be well if given nicotinic acid and some others will be helped. We think that these young people who are doomed to be in and out of mental hospitals for most of their lives, have a right to be given nicotinic acid even if medical men are sceptical." (p. 189).

In 1966 Hoffer and Osmond published their most spectacular paper (24). In this they claimed that nicotinamide adenine dinucleotide (NAD), the coenzyme derived from NA or NAA, made 11 out of

18 chronic schizophrenics, with illness ranging from 6 months to 30 years (averaging 9½ years), well within a few days after the oral administration of enteric coated tablets of NAD at a dose of 1.0 gm/day. The remainder of the patients improved significantly. When the NAD was discontinued after a few weeks of treatment the patients quickly relapsed. The dramatic results claimed in this paper attracted considerable attention. Attempts to replicate it were made quickly by several groups of investigators and invariably failed (41, 42, 43, 44, 45). We shall return to this point later in the review.

At the time of these first major publications, employing vitamin B_3, numerous papers concerning the effectiveness of phenothiazines were beginning to appear. Since these agents were more rapidly acting and indeed more highly publicized, it is not surprising that the Hoffer publications, which compared nicotinic acid with agents like ECT, barbiturates, and other non-specific treatments did not receive great recognition. In addition, however, the publications, especially the first, are difficult to read and follow, the criteria of patient improvement are not fully explicated, and the data are extremely difficult to assess. The results of the vitamin addition are also contaminated by the frequent use of ECT. The studies may also be criticized on the grounds of (1) the non-random selection of the
8 small numbers of the total population at risk in the hospitals studied; (2) the lack of clearly specified initial clinical diagnosis or systematic rating of patient behavior before and after treatment; (3) the failure to specify chronicity of illness; (4) nicotinic acid was never the only treatment given; (5) the number of patients in the ten-year follow-up sample was small and treatment and comparison groups were not matched as to pretreatment prognosis; (6) none of the Hoffer-Osmond studies compared nicotinic acid or the amide with the currently used phenothiazines, whose efficacy have been clearly demonstrated in large scale, well-controlled studies. In addition, the results of the first two nicotinic acid studies done by Hoffer give differing results which are hard to explain. In the first one, the patients received the drugs only in the hospital, did not improve significantly in the hospital, but had a lessened tendency to relapse for four years after discharge. In the second study, the reverse is true: there was an improvement in the hospital, but the subsequent relapse rate is the same.

Other reasons for scepticism among psychiatrists are based on the facts that the efficacy claims of megavitamin proponents are sometimes contradictory and their methodology sometimes questionable. For example, Hoffer often stresses the extremely rapid response to B_3 therapy, as can be seen from this extract from his 1962 paper in the *Lancet* (32): ". . . on May 28 we started him [a 17 year old

acute schizophrenic] on 5 grammes of niacin with 5 grammes of ascorbic acid daily, divided into four doses added to his tube-feeds. Next day tube-feeding was discontinued and ten days later he was described as 'almost normal'." (p. 317). But then Osmond (22) says: "Niacin did not work as quickly as the newer substances . . . [megavitamin therapy methods] are not often dramatic, but they work." And Denson (15) reports: "A preliminary assessment twelve months after the beginning of the trial did not show any significant difference in the performances of the two groups. A second assessment, carried out some eight months later, indicated that Group A [NAA] had done markedly better than Group B [placebo]." (p. 168).

Similar inconsistencies occur in the megavitamin literature regarding the efficacy of B_3 in the treatment of acute as opposed to chronic patients. For example, Osmond and Hoffer (32) state: ". . . subsequently niacin, given in much larger doses for many months on end, did not benefit other chronic schizophrenics, even when combined with E.C.T." (p. 317); and Hoffer similarly says (13): ". . . results were best with acute schizophrenic patients." (p. 499), and ". . . with chronic cases treatment was slow and required much larger doses of the vitamin for much longer periods of time, and many patients did not respond favourably." (p. 499). Saarma and Vasar (46), however, report that NA caused clinical improvement in 8 out of 24 chronic schizophrenics also receiving major psychotropic drugs, ameliorating dysfunction of "internal inhibitory activity," and cite *negative* findings for nicotinic acid in acute schizophrenics (47), which they explain by stating that acute patients have disturbed excitatory functions rather than dysfunction of inhibitory activity.

As for the issue of questionable methodology, three examples may be cited here; others will be presented in the sequel—especially with regard to patient selection and diagnostic procedure. The first concerns the follow-up evaluation procedure as reported by Hoffer in his 1957 paper (11). In this paper Hoffer states: "The follow-up study was designed to assess the patient's adjustment in terms of physical health, work, social activities, and family and interpersonal relationships. Contact every three months was maintained, preferably through direct interview with the patient or with relatives; when this was impossible, questionnaires and letters were mailed. In most cases, satisfactory contact was established." (p. 134). But then, on the very next page, Hoffer states: ". . . *a substantial proportion of control patients were not adequately followed in the community and their adjustment since discharge is not known* . . . When the adjustment rating is not available for a particular patient but his progress after discharge is adequately known, an *impressionistic* score is given . . ." (p. 135, italics ours).

The second example comes from a paper by Lino Chinaglia (48) wherein a clinical study of 14 acute schizophrenics is reported. Five of the 14, treated with NAA and ECT, had to be taken off the amide because of severe and intractable adverse reactions. The author, however, does *not* include these 5 patients in his outcome evaluations. Obviously, had he included these patients in his total outcome figures, his success claims would have appeared considerably less impressive.

Third, many of the statements and claims of megavitamin proponents are frequently proffered without any systematic evidence or documentation to support them. For example, Hoffer, in a broadside for public distribution published in 1965, says: "It [NA or NAA] does not cause any harm [during pregnancy] to babies. There is evidence that it can protect babies against the harmful effects of other substances." Unfortunately, Hoffer nowhere cites any such evidence. Furthermore, in the same broadside he recommends self-treatment, with no stipulation or recommendation that such self-medication be carried out under the guidance of a physician.

Attempts at Replication:

10 The fact that logical and methodological difficulties such as these abound in the megavitamin literature clearly makes objective evaluation and assessment of the validity of the treatment procedure extremely problematic. Furthermore, the evolution of the rationale, from a procedure emphasizing almost exclusively NA and NAA into a highly complex program utilizing virtually *all* the currently available agents in the pharmacological armamentarium, makes it extremely difficult to conduct replication trials that could legitimately and fairly attempt to assess megavitamin success claims with both specificity and comprehensiveness. Although the usage of B_3 remains the constant factor, and in the view of its advocates the crucial factor, this obviously does not necessarily mean that NA or the amide is actually the single most important aspect of the total treatment program. For example, ECT might be an equally significant variable. However, as megavitamin proponents so emphatically claim that it is the crucial factor, attempts at replication of the nicotinic acid work have usually dealt with the single addition of nicotinic acid or the amide to other specific treatment procedures.

Many attempts at replication have been made by numerous investigators. As stated previously, almost all of these have focused on the therapeutic utility of nicotinic acid or its amide alone or in combination with major psychotropic agents in the treatment of schizophrenia. Characteristic of these replicative studies is the reluctance to use ECT which is so commonly employed by mega-

vitamin advocates.

Ashby et al. (49) reported a double-blind study comparing NA, NAA and placebo in 39 chronic schizophrenic patients over a 26 week period and showed no difference between drug and placebo. Greenbaum (50) reported a double-blind study of 57 schizophrenic children who received nicotinamide 1 gm. per 50 lbs. of body weight or placebo for six months. No statistically significant differences were seen in the two groups as a result of the treatment. Meltzer et al. (45) showed that B_3 use did not increase efficacy of phenothiazines. McGrath et al. (51) studied 265 consecutive admissions for schizophrenia dividing them randomly into 132 who received nicotinamide at 3.0 grams daily for one year and 133 who received placebo for the same period. All patients received phenothiazines and participated in a general rehabilitation program. Patient characteristics included 15% who were ill for six months or less, 9% ill for six months to one year, 33% ill for five years and 43% ill for five years or more. No improvement was noticeable either after thirty days of treatment or after one year in either the acute or chronic patients.

Wittenborn et al. (52) have recently completed a double-blind study of the effects of NA in a group of 86 patients who were maintained on nicotinic acid or placebo for at least eighteen months. Seventy-five of these continued in treatment for two years. The patients were male. Their average age at the beginning of the study was 29 years and the average age at initial hospitalization was 25 years. The average amount of time spent in a hospital in five years prior to the initiation of the study was 7½ weeks. Forty-seven of the patients received nicotinic acid; 28 of them were controls. Nicotinic acid was limited to 3.0 gm daily. Psychotropic medicine or other treatments were employed at the discretion of the physician in charge. Thioridazine was recommended as the primary neuroleptic medication, but the treating physician was not held to this recommendation. The patients, though initially hospitalized at the beginning of the experiment, were usually discharged after several weeks so that the study for the most part was an outpatient inquiry. Social workers followed the patients at approximately monthly intervals and talked with families or other responsible associates about the patient's condition, use of medication and specific family problems relating to the patient and the niacin experiment. The patients returned to the clinic at monthly intervals for interviewing, psychological testing, evaluation of clinical state and assessment of use of medication. Laboratory tests to assess untoward metabolic effects were also conducted at monthly intervals.

The psychological ratings, under the supervision of Dr. Witten-

born, an exceptionally experienced researcher in the area of drug effects on mental illness, were unusually comprehensive and were designed to reflect four major areas in which disturbance might find expression: (1) symptomatic developments observable by others; (2) subjective discomfort as reported by the patient; (3) the quality of home and community adjustment as reported by the family or other close associates; and (4) performance as measured by simple perceptual-motor tests.

Although the data are not yet fully analyzed, several conclusions appear warranted. These are: (1) subjects on niacin tended to stay in the hospital longer, but the statistical significance of this is uncertain; (2) there was no difference in the rehospitalization rate of the niacin and control groups; (3) there was no difference in major tranquilizer use between the two groups; (4) both groups gained weight but no difference was apparent between the two groups; (5) both groups showed a slight reduction in diastolic blood pressure; (6) hyperkeratosis was noted in a significant number of patients receiving niacin, but this was not found in the control group; (7) in the psychological tests no significant differences were found between the two groups on clusters like anxiety, manic state, schizophrenic excitement, retardation, psychotic belligerence, paranoia, hebephrenia, intellectual impairment, etc; (8) in the tests designed to assess home and community adjustment the niacin group showed a slight trend in the direction of lessened sense of responsibility, less self-confidence and more complaints of not feeling well; (9) although the differences are small, in most of the comparisons home and community adjustment was more favorable in the control group than in the niacin group.

The field analysis of the data from the Wittenborn study is a formidable task and it is not yet complete. Those criteria which have thus far been fully analyzed show no appreciable differences between the control and the niacin groups over a two-year period. When these results are compared with the many sweeping statements of the megavitamin proponents, it is quite clear that they constitute a clear failure to replicate any general efficacy of niacin in the treatment of schizophrenia.

On the basis of a continuing *post hoc* scrutiny of his data Wittenborn (105) has recently reported several indications of an interactive relationship between features of patients' premorbid adjustment and their response to the addition of niacin to other drug treatments. These findings lead to an hypothesis that patients whose post-adolescent history showed no evidence of significant interpersonal relationships were unimproved by niacin. However, some patients whose pre-psychotic adjustment revealed periods of com-

mitted interpersonal participation, such as a marriage to an approving spouse, significant emotionally-dependent relationships with good friends, a responsible employment and self-support history, and a good heterosexual self-image, might be substantially improved and even restored to their premorbid level of adjustment after several months of treatment with the niacin-psychotropic drug combination. No such trends were found in the control group. Since this pattern of relationships was found in a *post hoc* search for such relationships, its possible significance will await cross validation in an independent sample.

The analysis of the data continues, but none of Wittenborn's findings encourage the expectation that vitamin B_3 is an effective treatment for the great mass of schizophrenics who are hospitalized for this disorder. Although Wittenborn considers his data to be consistent with the possibility that as many as ¼ of his schizophrenic population (those with good premorbid adjustment) might be benefitted by the addition of niacin to the psychotropic drug treatment, the fact that he finds no significant difference between the total control group and the total vitamin group implies that a fraction of his experimental population may have had their progress impeded by the vitamin addition. Wittenborn also questions the aptness of the schizophrenic designation for those patients with the good premorbid history that are identified as improving with the vitamin.

The most thoroughgoing attempts at replication of the vitamin B_3 studies have been carried out in the Canadian Mental Health Association collaborative studies (53, 54, 55, 56). These studies, involving several mental hospitals, a large number of patients, and a diverse staff of psychiatrists, have been carried out under the general supervision of Drs. Ban and Lehmann from McGill University. These workers selected from the general conclusions of the megavitamin proponents several specific hypotheses which were directly testable. (e.g., patients on NA require less phenothiazines). These are shown in the following table, which shows the overall strategy of the McGill group, emphasizing the general hypotheses, the experimental design to test them and the present status of the research.

TABLE 1

THE TWELVE CLINICAL TRIALS OF THE CANADIAN MENTAL HEALTH ASSOCIATION COLLABORATIVE STUDY

	General Hypothesis	Design	Present Status
I	Nicotinic acid has a beneficial action over and above the effects achievable by standard treatments	1. Placebo-controlled	1. Completed
		2. Standard-controlled	2. To be started
		3. Placebo-controlled; combined with phenothiazines in acute patients	3. Completed
		4. Placebo-controlled; combined with phenothiazines in chronic patients	4. Completed
		5. Placebo-controlled; five year follow-up	5. In progress
II	Therapeutic efficacy of nicotinic acid is increased by the administration of ascorbic acid, pyridoxine, or d-penicillamine	6. Placebo-controlled; combined with ascorbic acid	6. In progress
		7. Placebo-controlled; combined with pyridoxine	7. Completed
		8. Placebo-controlled; combined with d-penicillamine	8. To be started
III	The presence of the "mauve factor," "pink spot," or a bufotenin-like substance in the urine indicates a more favorable therapeutic outcome with nicotinic acid	9. Comparison groups; "mauve spot" present or absent	9. In progress
		10. Comparison groups; "pink spot" present or absent	10. To be started
		11. Comparison groups; bufotenin-like substances present or absent	11. To be started
IV	The exacerbation of psychopathology induced by the associated administration of a methyldonor and an MAOI in schizophrenia can be prevented or counteracted by nicotinic acid administration	12. Placebo-controlled	12. Completed

This complex set of experiments is still in progress, but several interesting reports have been published (53,54,55,56,57). The results thus far strongly suggest that in the dosage of 3.0 gm/day NA has no therapeutic effect and may even have a negative effect in unselected groups of schizophrenic patients. The following findings support this conclusion.

From Study No. 1: *the overall therapeutic efficacy of nicotinic acid as the sole medication in newly admitted schizophrenic patients is not superior to the overall therapeutic efficacy of an inactive placebo.* In fact, the majority of newly admitted schizophrenic patients — in a placebo controlled two-year study with 30 patients — could not be sufficiently controlled with high dosages — 3000 to 8000 mg per day — of nicotinic acid administration. Further analysis of data revealed that during the two-year investigational period — regardless of whether the patients were kept on the project or not — the average number of days spent in hospital was lowest in the placebo (211 days) and highest in the nicotinamide treated group (353 days). However, the number of days spent in hospital was only slightly higher — 214 days — in the nicotinic acid than in the placebo treated patients (58).

From Study No. 3: *the overall therapeutic efficacy of nicotinic acid as an adjuvant medication in newly admitted schizophrenic patients is inferior to the overall therapeutic efficacy of an inactive placebo.* In fact, the addition of nicotinic acid, in the dosage of 3000 mg per day, to regular phenothiazine treatment — in a placebo controlled six months study with 30 patients — prolonged the duration of hospital stay and increased the amount of neuroleptic medication required in treatment (53).

From Study No. 4: *the overall therapeutic efficacy of nicotinic acid — in the dosage of 3000 mg per day — as an adjuvant medication in chronically hospitalized schizophrenic patients is inferior to the overall therapeutic efficacy of an inactive placebo.* In fact, in a one-year placebo-controlled study with 30 patients, the active treatment groups fared worse than the placebo group by all measures of assessment. The least improvement and the greatest amount of deterioration was seen in the nicotinic acid group. Moreover, it was shown that patients in the placebo group required less increase in their concomitant phenothiazine medication than patients in the two active treatment groups (55,56).

From Study No. 7: *the overall therapeutic efficacy of combined administration of nicotinic acid and pyridoxine as an adjuvant medication in chronically hospitalized schizophrenic patients is inferior to the overall therapeutic efficacy of the component drugs (59).*

From Study No. 12: *nicotinic acid in the dosage of 3000 mg per day — can neither prevent nor counteract the psychopathology induced by the combined administration of a monoamine oxidase inhibitor (tranylcypromine) and methionine.* In fact, during the two weeks of methionine (20000 mg per day) administration, there was a considerably greater increase in psychopathological symptoms — expressed in mean total scores of the Brief Psychiatric Rating Scale (BPRS) — in the nicotinic acid — than in the placebo-treated group (54).

The negative findings in these carefully controlled studies are clearly at variance with the results claimed by the megavitamin proponents for the utility of nicotinic acid or nicotinamide in the treatment of schizophrenia. Specifically there is no support for claims about (a) decreased time in the hospital, (b) a lowered requirement for phenothiazines and (c) a quick response in acute schizophrenics. On the other hand, they are fully consonant with the studies of McGrath (51) and Wittenborn et al. (52) in showing no therapeutic utility.

IV. PELLAGRA, SCHIZOPHRENIA AND THE QUESTION OF NAD

In the 1957 publication claiming the effectiveness of nicotinic acid in the treatment of schizophrenia, Hoffer et al. (11) offered nine speculations as to mode of action of the vitamin. Their first choice of mechanism was that nicotinic acid functioned as a methyl acceptor reducing adrenochrome formation. Their ninth choice was that of the psychological placebo effect. Their eighth choice was that of vitamin deficiency. At that point, the authors stated "the psychoses (sic) associated with pellagra does in many ways resemble the schizophrenic psychosis except that it contains qualities of toxic confusion. However, the incidence of avitaminosis among schizophrenic persons is no greater than among the general population. Dosages adequate to treat any unknown deficiency are without effect on schizophrenia. It may be concluded, therefore, that this factor is unimportant." (p. 150).

In 1970, Hoffer (8) puts incipient cerebral pellagra as his top choice for the etiology of schizophrenia and suggests that the coenzyme (NAD) deficiency is corrected by nicotinic acid. In this paper he emphasizes the similarities between the two conditions and their patterns of onset. Initial symptoms of pellagra which he reports include headache, irregular appetite, depression, and debility. As the disease develops, these symptoms become exacerbated and feelings of anxiety and depression become prominent. In its advanced stages, profound melancholia, impairment of faculties and senses, and dementia set in. Associated with this process are thought disorders, both in content and process, pathological changes in mood, and bizarre, inappropriate, and antisocial behavior. Hoffer concludes that this is an excellent description of early schizophrenia and a bit further on states, ". . . it is clear that there are no clinical grounds for separating these two diseases. The distinction is artificial. . . ." (p. 523).

It was in 1938 that Elvehjem and his associates (60) isolated nicotinic acid from liver and proved that it cured and prevented "black tongue" in dogs. Subsequently, three independent groups of investigators (61,62,63) established the efficacy of nicotinic acid in the treatment of human pellagra. The recognition that nicotinic acid

deficiency produced a typical somatic illness with varying psychopathological symptoms, which were cured by nicotinic acid administration, was one of the fundamental discoveries in modern biological psychiatry. It was the first time that naturally occurring psychopathological symptoms could be *experimentally induced* — by restricting the nicotinic acid supply; *counteracted* — by nicotinic acid administration; and *studied* in the laboratory. By 1945, it was clearly shown that a variety of psychiatric disorders may develop with nicotinic acid deficiency (64). Medlicott (65) subdivided these conditions into two clinical categories: a) those due to chronic deficiency and b) those due to acute deficiency. He provided evidence that chronic mild deficiency may manifest itself as a neurasthenic syndrome or, in more severe deficiency, as typical pellagra with its associated dermatitis, diarrhea and dementia; while acute nicotinic acid deficiency may result in a state of confusional exhaustion, profound stupor and coma alone, or, as in nicotinic acid deficiency encephalopathy (66), associated with characteristic neurological manifestations, e.g., cogwheel rigidity, grasping and sucking reflexes.

Similarly, by 1955, it was clearly shown that there is a variety of psychiatric symptoms, e.g., depression, delirium, dementia, and a variety of psychiatric disorders in which nicotinic acid has a therapeutic effect. Gregory (67) subdivided these conditions into three categories: a) those in which therapeutic effects are attributed wholly to the control of the nutritional deficiency (i.e., pellagra, pellagra sine pellagra, or nicotinic acid deficiency encephalopathy); b) those in which thrapeutic effects are attributed only in part to the control of the nutritional deficiency and in part to the "mass action" of nicotinic acid (i.e., organic psychoses associated with malnutrition, alcoholism and/or senescence); and c) those in which therapeutic effects are unrelated to the control of nutritional deficiency, but are attributed to the vasodilation produced by nicotinic acid (i.e., organic brain dysfunction following cerebral trauma, hypoxic episodes and certain functional depressive and anxiety reactions).

Since pellagra is today virtually unknown in the United States and Canada, one must take recourse for comprehensive descriptions of the illness from clinicians writing in the 1940's and earlier. In all these descriptions of the disease, somatic symptoms are invariably emphasized. Weight loss, dermatitis, glossitis, paraesthesias, and convulsions are typical. Major (66) devotes a chapter to the earliest descriptions of pellagra made in the 19th and 18th centuries. Sydenstricker, Sebrell, Goldberger, and Spies, who were the prominent investigators of pellagra in the 1920's and 30's, also emphasize the somatic aspects of the illness. Psychological aspects are minimized, and, when they occur, tend to be of the organic reaction types

stressed above by Medlicott and Gregory. Similarly, Henderson and Gillespie (69) state that only 4 to 10 percent of pellagrins show mental symptoms and state that the mental symptoms associated with pellagra are usually either in the nature of a depressive state, a chronic organic reaction, or a delirium. The last is the most frequent. The depression is largely based on the fact that the patient realizes that he is suffering from a severe physical illness while the delirium is of the usual toxic type. Russell Brain (70) speaks of the initial gastro-intestinal changes and cutaneous lesions and emphasizes that nervous changes develop later. Many abnormal states may occur; these may include mania and melancholia and often the terminal state is dementia. Epileptic fits are not uncommon. Visual impairment and diplopia may occur. Sydenstricker (71) carefully describes the clinical manifestations of pellagra and also emphasizes the dermatitis and gastro-intestinal symptoms. He agrees, however, that in a chronic partial deficiency state, mild psychic disorders may precede other manifestations by weeks or months. Slight mental retardation, loss of memory for recent events, apprehension, confabulation, depression, or mild delusional states may recur intermittently for months or years. When nicotinic acid is added, psychic manifestations of all grades are cured or greatly improved. Sydenstricker and Cleckley (72) described the effect of nicotinic acid in stupor, lethargy, and various other psychiatric disorders. They also emphasized that subclinical and mild pellagrins may suffer from vague complaints suggestive of neurasthenia or hypochondriasis. Jolliffe and co-workers (66) report a B_3-responsive encephalopathic syndrome characterized by marked clouding of consciousness and severe psychomotor disturbance which is greatly benefited or cured by the administration of nicotinic acid. In their own series of 38 cases, Sydenstricker and Cleckley (72) were led to conclude that a significant number of patients whose psychiatric status suggests the diagnosis of toxic psychosis or exhaustion delirium may be relieved of their symptoms by the administration of nicotinic acid. Not all of these cases show typical somatic signs of pellagra, and they also suggest that cases which show unexplained clouding of consciousness deserve a therapeutic trial of nicotinic acid.

From these various descriptions of the symptoms associated with nicotinic acid deficiency, it is quite clear that the psychological manifestations vary greatly depending upon the degree of deficiency and whether it is acute or chronic. The range of symptoms may vary from neurasthenia to toxic delirium and coma. Mood disorders are not infrequent. Clouding of consciousness characteristic of an organic brain syndrome is very prominent. It is rare, however, to

find mental symptoms without associated somatic symptoms involving the skin or gastro-intestinal tract.

It is therefore quite clear that clinical resemblance of nicotinic acid deficiency to schizophrenia is minimal and that features of an organic brain syndrome are prominent. The original opinion stated by Hoffer in 1957 seems more accurate than his position in 1970. Hoffer attempts to deal with the apparent shift in his position by proposing that classical somatic pellagra is due to a combined deficiency of vitamin B_3 and tryptophan. He tends to attribute the somatic symptoms of pellagra to the tryptophan deficiency and the psychic ones to the niacin deficiency. While it is true that there is a well established relationship between tryptophan and niacin, insofar as one of the several metabolic directions which tryptophan may take is in the production of niacin, the fact remains that classical pellagra can be treated with niacin even without tryptophan supplementation. Thus, there is no evidence whatsoever to support the Hoffer speculation that the tryptophan deficiency results in somatic symptoms while the niacin deficiency results in the psychic ones.

The question of whether or not schizophrenia resembles pellagra in that there is a co-enzyme deficiency of NAD is readily testable. NAD can be assayed in red blood cells. It tends to be low in pellagra
20 (73), and it is readily elevated following the administration of nicotinic acid. Evidence for diminished NAD content in the blood of tissues of schizophrenics has never been reported by any of the proponents of the pellagra-schizophrenia hypothesis. Indeed one study (74) showed that the blood of schizophrenic patients has a normal concentration of pyridine nucleotides (NAD and NADP).

Furthermore, the report by Hoffer and Osmond (24) that NAD was rapidly effective in schizophrenia has not only been thoroughly refuted by several groups of clinical investigators, but it was *a priori* implausible because if NAD behaves like other co-enzymes, it would likely not penetrate intact into cells and hence should be no more effective than the niacin which it contains. Typically, co-enzymes are synthesized within cells from their constituents. This has been shown for thiamine pyrophosphate, and there is no reason to think that an even more complex and fragile molecule like NAD would behave differently. Finally, while mononucleotides may penetrate the blood brain barrier and cell walls, it is highly unlikely that dinucleotides like NAD would do so.

The Hoffer-Osmond claims about NAD have been easily tested clinically because they were so specific, rapid and dramatic. In their report on the efficacy of NAD (24) chronic schizophrenics averaging 9½ years of illness were reported to become well or markedly improved in a matter of a few days following NAD administration. The

improvement was reported to last only a bit longer than the period during which the coenzyme was administered. Relapses occurred shortly after discontinuation of medication.

As to why there should be an NAD deficiency, Hoffer and Osmond suggested several possibilities: (1) there might be a nicotinic acid deficiency in the diet, or perhaps a deficiency of adenosine triphosphate, a cofactor for the synthesis of NAD; (2) there might also be excessive destruction of NAD because of ". . . excessive consumption of toxins like alcohol by in vivo production of hallucinogens like adrenochrome or by excessive activity of NADase." (24, p. 88). Of these, the authors appear to favor the concept that the adrenochrome would ". . . overload the enzyme system synthesizing NAD . . . [so that] Eventually there could be a major and relatively permanent deficiency in the synthesis of NAD." (24, p. 88). There is no evidence to support this.

Clinical replications were quickly tried and have, in all instances, failed. A most systematic study is reported from Rockland State Hospital by Kline et al. (41) where 20 schizophrenics were matched in 10 pairs and given NAD or placebo for two months in a double-blind program. Pre- and post-drug evaluations were made by filmed and recorded interviews, in addition to three different psychological parameters including the HOD (Hoffer-Osmond Diagnostic) test. Both groups improved, though insignificantly. Patients on placebo improved more as measured by interviews.

Gallant et al. (42) used NAD in 10 severely chronic schizophrenics for 49 days with no significant improvement on psychological testing or interview. Kline et al. (43) treated 3 acute schizophrenics with NAD without benefit, and Gottlieb (44) tried NAD intravenously in 4 chronic schizophrenics and failed to detect any change. Hoffer was critical of the Kline study, because he felt the medication used was inadequately prepared, but had no such complaint about the Gallant study. Meltzer and his colleagues (45) went to some considerable pains to preserve the NAD in special capsules and to demonstrate the elevation of NAD in serum following its administration. Nonetheless, this carefully controlled study likewise showed no significant positive benefit from the use of NAD.

In summary, then, evidence that NAD is effective has been refuted clinically, and evidence of an NAD deficiency in schizophrenia lacks both biochemical and clinical support. In contrast to many of the megavitamin claims which are confounded by questions of severity of illness, duration of niacin treatment, and the use of supplementary nutritional and drug treatments, the claims for NAD were dramatic and claimed almost immediate relief of all symptoms with most of the patients reported well within a few days. The clarity of

these claims made replication quick and precise. The total failure to obtain positive findings when the therapeutic procedure was attempted by other investigators diminishes the credibility of the niacin advocates as critical clinical researchers. But it does not fully eliminate the possibility that nicotinic acid might still be effective therapeutically as a vitamin or as a pharmacological agent affecting cerebral blood flow or correcting faulty transmethylation mechanisms. It is interesting to note that no additional reports of positive findings with NAD even by megavitamin advocates have appeared since the initial report in 1966.

V. THE DIAGNOSIS OF SCHIZOPHRENIA, PATIENT SELECTION, AND SPECIFIC PHASE-TREATMENT PROGRAMS OF ORTHOMOLECULAR PSYCHIATRISTS

It is axiomatic that an accurate assessment of the results of any medical treatment requires a high level of agreement that the patient under treatment really has the illness which the physician states he has. In the case of schizophrenia there is usually satisfactory agreement among psychiatrists and psychologists when the illness is sufficiently severe to require hospitalization, and the agreement increases with repeated hospitalizations. But in ambulatory cases or acute illnesses requiring a first hospitalization the diagnosis is much more difficult, and disagreement is not unusual. For example, patients with a diagnosis of manic-depressive illness especially appear increasingly schizophrenic with each hospitalization (75). Latent schizophrenia (76), pseudoneurotic schizophrenia (77), borderline state (78) and schizoid personality (79) are other difficult diagnostic categories. In general, in such patients the symptoms or behavior may not appear to be schizophrenic. Rather, they may range from obsessional thinking, panphobia, pan-anxiety and hypochondriasis, to eccentricity, fanaticism and hypersensitivity. A definitive diagnosis in such patients frequently must be made over time since they are more likely to develop an overt psychosis episodically (77). Errors in the diagnosis of such conditions occur in two directions. Patients with such conditions may be underdiagnosed or overdiagnosed. They may be called schizophrenic when they are not or may be diagnosed by some other term when their long-range outcome may be clearly schizophrenic.

Regardless of the difficulty in diagnosing particular cases at particular times there continues to be general acceptance of Bleuler's (76) definition and criteria for the schizophrenias.

The primary symptoms consist of a diminution of associative affinities — a thought disorder. Secondary but fundamental disturbances include the affective disturbance of anhedonia, the morbid ambivalence and the autistic withdrawal from reality. Psychological tests such as the MMPI or the Wittenborn Scales (23) for the diag-

nosis of schizophrenia take these symptoms into consideration. Even with the best clinical judgment and the most sophisticated psychological testing errors still are made. Thus, Wittenborn (52) in his attempts to replicate the claims of megavitamin therapy of schizophrenia initially accepted some patients into his study and later dropped them when he found them to be not schizophrenic.

The primary symptoms consist of a diminution in associative affinities, sometimes called splitting of associations, cognitive slippage or a schizophreniform cognitive mode (75). This is usually manifested as a fundamental disturbance in the perception or evaluation of reality that cannot be explained on the basis of toxic etiologic agents (such as dextro amphetamine), known organic brain diseases (such as paresis), severe depression or elation (as in manic-depressive illness) or special cultural or educational influences. Secondary but fundamental disturbances of Bleuler include anhedonia, a morbid ambivalence and autistic withdrawal from reality. Other secondary accessory symptoms like hallucinations, delusions, illusions, catatonic symptoms, pan-anxiety, depersonalization, chaotic sexuality, etc. may also occur but are not prognostic and are not unique to schizophrenia. The necessary, but not always sufficient, condition for the diagnosis of schizophrenia is in the cognitive-perceptual area and consists of a fundamental difficulty in the perception or evaluation of reality.

Despite the many difficulties involved in the selection of a patient population of schizophrenics and the equally large difficulties in the assessment of change, methods have been developed which are sufficiently reliable to measure drug effects in schizophrenia. Klein and Davis (80) summarize the extensive literature on clinical drug trials with anti-psychotic drugs. They emphasize the need for well-defined and characterized treatment populations, double-blind studies, multiple rating scales and appropriate statistics. Ban (103) has recently summarized the large number of sophisticated psychological tests and rating scales which have been extensively employed in the diagnosis of schizophrenia, the assessment of its severity and the demonstration of change following treatment. Illustrative well-designed studies include the NIMH-Psychopharmacology Service Center collaborative studies (81, 82) and the Veterans Administration studies (83). Similar sophisticated studies to those utilized in drug evaluation have been used by Wittenborn (52) and the Canadian Mental Health Association group (53, 54, 55, 56) on the assessment of the value of niacin, with negative results.

In the initial studies reported by Hoffer and Osmond in 1957, the characteristics of the patients are not clearly defined, but they were apparently sufficiently ill to require hospitalization and ECT.

Apparently they included cases of early onset pseudo-neurotic schizophrenia and previously treated patients who had suffered a relapse. It was with these patients that the first double-blind studies were performed comparing the effectiveness of conventional somatic treatments such as ECT and barbiturates (but not the major tranquilizers) with and without vitamin B_3. The conclusion reached at the end of these studies was the relatively modest claim that "When used in adequate dosages, nicotinic acid and nicotinamide materially contribute to the recovery of schizophrenic patients." (11, p. 155).

In later publications by this group the clinical criteria for the diagnosis of schizophrenia have not been further specified, double-blind experiments have been discontinued and greater dependence has been placed upon a simple psychological card-sorting test (the Hoffer-Osmond Diagnostic or HOD test) and upon a chemical urinary test for a mauve factor. These tests are employed in the diagnosis of schizophrenia, in the phasing of the treatment and in the rating of the efficacy of their treatment program. Both tests were developed on the basis of their conceptual view of schizophrenia as a metabolic disorder with associated perceptual defects.

The HOD test first appeared in a paper by Hoffer and Osmond in 1961 (84) as a result of a search for "an ideal diagnostic test for general clinical use in schizophrenia." Such a test should ". . . make a complete separation between normal subjects and schizophrenic patients. . . . It should measure the severity of the illness. . . . Quantitatively . . . it should be applicable to most patients — over 90%." (p. 308).

Apparently Hoffer feels that the HOD test approximates these criteria. In a monograph devoted to a description of his diagnostic and treatment procedures (18) he states:

> The most important diagnostic tool is clinical judgment, plus an awareness that schizophrenia is much more prevalent than is generally believed. Since megavitamin B-3 therapy works best with early cases it is vital that diagnosis and, therefore, treatment begin early. The diagnostic category described by Polatin and Hoch as pseudoneurotic schizophrenia is a very good one, since it forces the physician to think about schizophrenia early. One must not await until classical thought disorder, and hallucinations appear. By then the patients are chronic and treatment is more difficult. John Conolly (1830) described psychosis as a disorder of perception plus an inability to judge whether these changes are real or not. For reasons which are unknown to me, this excellent operational definition has been lost for over a century, but it is still one of the most fruitful guides to early diagnosis.

He then goes on to discuss the importance of the HOD test and the test of mauve factor on the urine, which, he states are important objective tests to confirm the diagnosis of schizophrenia: "In my opinion HOD has provided every physician with a tool for detecting early schizophrenia easily; if it is combined with therapy to be described here (it) will allow every physician to treat successfully the majority of his schizophrenic patients and many who are depressed and anxious, but do not yet show typical features of schizophrenia." (p. 7).

Elsewhere, even more exaggerated claims are made for the diagnostic, course of treatment, and follow-up evaluation efficacy of the HOD test. For example, Hoffer, in his paper "Treatment of Schizophrenia With a Therapeutic Program Based upon Nicotinic Acid as the Main Variable" (85) says, "I have used the total score (TS) of the HOD test as the criterion for clinical improvement since it was much more accurate than our clinical assessment." Similarly, Hawkins, Bortin and Runyon (10) make the extraordinary statement: "The severity of the illness are (sic) its course and response to treatment is monitored by the HOD (Hoffer-Osmond Diagnostic), EWI (Experimental World Inventory), and OIT (Organic Integrity) tests. These have been demonstrated to be more accurate than clinical diagnosis and highly efficient tools." (p. 518). Unfortunately, all the references cited by Hawkins in support for the claim of such "demonstration" are papers by other megavitamin therapy proponents.

The following excerpt from Hoffer and Osmond's paper (84) gives the questions and the scoring procedure for the use of the HOD test.

Description of the HOD Test

Each question is typed on a small white card about 3" x 5". Each card is numbered on the back. The questions are shown in Table I.

TABLE I

VISUAL PERCEPTION

1. People's faces sometimes pulsate as I watch them.
2. People's faces seem to change in size as I watch them.
3. People's eyes seem very piercing and frightening.
4. People watch me a lot more than they used to.
5. People watch me all the time.
6. I feel rays of energy upon me.
7. Most people have halos (areas of brightness) around their heads.
8. Sometimes I have visions of people when I close my eyes.
9. Sometimes I have visions of people during the time when my eyes are open.

10. Sometimes I have visions of animals or scenes.
11. Sometimes I have visions of God or of Christ.
12. Sometimes the world seems unreal.
13. Sometimes I feel very unreal.
14. When I look at things like tables and chairs they seem strange.
15. When I look at people they seem strange.
16. Often when I look at people they seem to be like someone else.
17. Now and then when I look in the mirror my face changes and seems different.
18. My body now and then seems to be altered—too big or too small, out of proportion.
19. Sometimes the world becomes very bright as I look at it.
20. Sometimes the world becomes very dim as I look at it.
21. Sometimes when I read the words begin to look funny—they move around or grow faint.
22. Sometimes when I watch TV the picture looks very strange.
23. Sometimes I feel there is a fog or mist shutting me away from the world.
24. Sometimes objects pulsate when I look at them.
25. Pictures appear to be alive and to breathe.
26. I often see sparks or spots of light floating before me.
27. My hands or feet sometimes seem much too large for me.
28. I sometimes feel that I have left my body.
29. I often feel I have left my body.

AUDITORY PERCEPTION

30. My sense of hearing is now more sensitive than it ever has been.
31. I now have more trouble hearing people.
32. I often have singing noises in my ears.
33. I often hear or have heard voices.
34. I often hear or have heard voices talking about or to me.
35. I have often felt that there was another voice in my head.
36. I have often heard strange sounds, e.g. laughing, which frighten me.
37. I have heard voices coming from radio, television, or tape recorders talking about me.

TACTILE PERCEPTION

38. My sense of touch has now become very keen.
39. I sometimes have sensations of crawly things under my skin.
40. I sometimes feel rays of electricity shooting through me.
41. Some of my organs feel dead.
42. I sometimes feel my stomach is dead.

43. I sometimes feel my bowels are dead.
44. I sometimes feel I am being pinched by unseen things.
45. I now have trouble feeling hot or cold things.
46. I sometimes feel strange vibrations shivering through me.

TASTE PERCEPTION

47. Some foods which never tasted funny before do so now.
48. I can taste bitter things in some foods like poison.
49. Foods taste flat and lifeless.
50. I have more difficulty tasting foods now.
51. Water now has funny tastes.

TIME PERCEPTION

52. I can no longer tell how much time has gone by.
53. The days seem to go by very slowly.
54. Some days move by so quickly it seems only minutes have gone by.
55. I have much more trouble keeping appointments.
56. I have much more trouble getting my work done on time.

OLFACTORY PERCEPTION

57. Things smell very funny now.
58. My body odor is much more noticeable than it once was.
59. My body odor is much more unpleasant now.
60. I sweat much more now than when I used to.
61. I can no longer smell perfumes as well as I used to.
62. Foods smell funny now.

THOUGHT

63. At times my mind goes blank.
64. At times my ideas disappear for a few moments and then reappear.
65. I am bothered by very disturbing ideas.
66. My mind is racing away from me.
67. At times I am aware of people talking about me.
68. There are some people trying to do me harm.
69. There is some plot against me.
70. I have a mission in life given to me by God.
71. At times some other people can read my mind.
72. I can read other people's minds.
73. At times when I come into a new situation, I feel strongly the situation is a repeat of one that happened before.
74. I now become easily confused.
75. I am now much more forgetful.
76. I now am sick.
77. I can not make up my mind about things that before did not trouble me.
78. My thinking gets all mixed up when I have to act quickly.

79. I very often get directions wrong.
80. Strange people or places frighten me.
81. People are watching me.
82. A cow is like a horse because they are both in Saskatchewan, not because they are both animals.
83. A cow is like a horse because they are animals, not because they are in Saskatchewan.
84. A chair is like a table because they have four legs, not because they are usually used together.
85. A chair is like a table because they are usually used together rather than because they both have four legs.
86. A dress is like a glove because they belong to women rather than because they are articles of clothing.
87. A dress is like a glove because they are articles of clothing rather than because they are owned by women.
88. A pen is like a pencil because they are like sticks.
89. A pen is like a pencil because they are both used for writing rather than because they both are like sticks.
90. An orange is like a banana because they both have skins rather than because they are fruit.
91. An orange is like a banana because they are fruit, not because they both have skins.
92. An axe is like a saw because they have handles, rather than because they are tools.
93. An axe is like a saw because they are tools, rather than because they have handles.
94. The eye is like the ear because they are on the head rather than because they are sense organs.
95. The eye is like the ear because they are sense organs rather than because they are on the head.
96. Air is like water because they are both cold rather than because they are needed for life.
97. Air is like water because they are needed for life rather than because they are both cold.
98. Praise is like punishment because they both start with p rather than because they are given to people.
99. Praise is like punishment because they are both given to people rather than because they start with the letter p.
100. A fly is like a tree because they both require humans rather than because they are living things.
101. A fly is like a tree because they both are living things rather than because they both require humans.

FEELINGS

102. I very often am very tired.
103. I very often suffer from severe nervous exhaustion.
104. I very often have great difficulty falling asleep at night.
105. I usually feel alone and sad at a party.

106. I usually feel miserable and blue.
107. Life seems entirely hopeless.
108. I am very painfully shy.
109. I am often misunderstood by people.
110. I have to be on my guard with friends.
111. Very often friends irritate me.
112. My family irritates me very much.
113. I am often very shaky.
114. I am constantly keyed up and jittery.
115. Sudden noises make me jump or shake badly.
116. I often become scared of sudden movements or noises at night.
117. My hands or feet sometimes feel far away.
118. My hands or feet often look very small now.
119. Cars seem to move very quickly now. I can't be sure where they are.
120. When I am driving in a car objects and people change shape very quickly. They didn't used to.
121. I often hear my thoughts inside my head.
122. I often hear my own thoughts outside my head.
123. I hear my own thoughts as clearly as if they were a voice.
124. My bones often feel soft.
125. Cigarettes taste queer now.
126. Other people's cigarette smoke smells strange—like a gas.
127. The world has become timeless for me.
128. Time seems to have changed recently, but I am not sure how.
129. Other people smell strange.
130. People look as if they were dead now.
131. I feel as if I am dead.
132. People are often envious of me.
133. Many people know that I have a mission in life.
134. People interfere with my body to harm me.
135. People interfere with my body to help me.
136. People interfere with my mind to harm me.
137. People interfere with my mind to help me.
138. I know that most people expect a great deal of me.
139. Lately I often get frightened when driving myself in a car.
140. I get more frightened now when I am driven in a car by others.
141. I don't like meeting people—you can't trust anyone now.
142. More people admire me now than ever before.
143. Most people hate me.
144. I find that past, present and future seem all muddled up.
145. I am not sure who I am.

In giving the test, the cards are first well shuffled and then handed to the subjects with two cardboard boxes, one labelled

"true" and the other labelled "false." The subject is told that this is not an intelligence test but a symptom check list. The questions on the card apply to him and must be placed in either the true box or in the false. No doubtful cards are allowed. The test can be run in an office or the patient may take it to his room. Cards placed in the "true" box are marked with a circle on the scoring sheet as shown in Table II.

TABLE II

Date .....

Name .....

Age ..... Sex .....

Diagnosis .....

Encircle all Cards in True Box

A-(1)	26	51	76	101	126
(2)	27	E-52	77	I-102	127
3	28	53	78	103	(128)
4	29	54	79	104	(129)
5	B-30	55	80	105	(130)
6	31	56	81	106	131
7	32	F(57)	H-82—2	107	132
8	33	58	83	108	133
9	(34)	59	84—1	109	(134)
10	35	60	85	110	135
11	(36)	61	86—1	111	(136)
12	(37)	62	87	112	137
13	C-38	G-63	88—1	113	138
(14)	39	64	89	114	(139)
15	40	65	90—1	115	140
16	41	66	91	116	(141)
17	42	67	92—2	(117)	142
18	43	(68)	93	(118)	(143)
19	(44)	69	94—1	(119)	144
20	45	70	95	(120)	(145)
21	46	71	96—1	(121)	
22	D-47	(72)	97	(122)	
23	48	73	98—1	123	
24	49	74	99	124	
25	50	75	100—2	125	

No attempt was made to develop a scoring system until about 150 normal and nonschizophrenic subjects had been tested. Cards which had never been placed in the true box or had been placed there only once were given a weighted score of 5.

The question cards are divided in the following way:

A. Visual Perception
Cards 1-29, 117-120 inclusive, 130, 139 and 140.

B. Auditory Perception
Cards 30-37 and 121-123 inclusive.

C. Tactile Perception
Cards 38-46 and 124.

D. Taste Perception
Cards 47-51, 125 and 126

E. Time Perception
Cards 52-56, 127, 128 and 144

F. Olfactory Perception
Cards 57 to 62 and 129

G. Changes in Thought
Cards 63-81, 131-139, 141-143 inclusive and 145

H. Cards 82-101 inclusive, measures the way in which subjects classify things. (If someone says that a pen is like a pencil because they are sticks, this is called a visual classification, but if he states they are alike because they are both used for writing, then he is using a functional classification. Either classification is correct, but each implies very different rules for classifying. A correct and consistent functional classification is one in which all the odd numbers are scored true and all the even ones false. In the same way, a correct and consistent visual classification is one in which all the odd numbers are scored false and all the even numbers true. If two cards of one set, say 84 and 85, are scored the same way, this is noted as an inconsistency. The maximum consistency score is ten and the minimum zero [i.e., all 20 cards placed in the same box].)

I. Affect
Cards 102-116

The Total Score (TS) is compiled by: (a) scoring each number on Table II which has a circle around it as 5, i.e., if cards 1 and 37 were both in the true box, 10 is added to the score; (b) one point is given for every other card said to be true, excluding category H; and (c) one or two is given for each number under H as indicated in Table II.

The Paranoid Score (PS) is obtained by giving one point for each of these cards: 4, 5, 34, 67, 69, 81, 132, 134, 135, 136, 137, 141, 142, 143. The highest paranoid score possible is 15.

> The Perceptual Score is obtained by adding up all the cards said to be true for the following numbers: 1, 2, 4, 5, 7, 9, 10, 11, 12, 13, 14, 15, 17, 18, 21, 23, 24, 27, 28, 29, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 48, 51, 52, 54, 57, 62, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 144. These questions were selected as being likely to be associated with instability in the external world and so would probably interfere with social functioning. Constancy of perception is probably of greater importance for normal living than any other perceptual variable. (pp. 308-312).

The HOD test is subject to several criticisms. (1) Both Ban (56) and Wittenborn (52) find that many acute and chronic schizophrenics are too ill to perform the test. (2) To the best of our knowledge the HOD test has never been systematically studied for validity and reliability by checking it against history, clinical diagnosis, spontaneous change on repeated testing, changes in response to treatment compared to clinical course, etc. The developers of the HOD test used 150 subjects and on the basis of group mean scores claimed that it differentiated schizophrenics from neurotics. No data were offered on measures of variability or the probability of the differences being due to random variation alone. (3) The vagueness and ambiguity of the questions of frequency of occurrence, "sometimes," "now and then" and "at times" render precise evaluation of the test results extremely problematic. (4) Attempts by other workers to establish the validity of the test for the differential diagnosis of schizophrenia have led to conflicting results. One study (86) noted that the test scores were significantly different between schizophrenics, neurotics and character disorders but not between schizophrenics and other psychotics. Another study (87) found in a group of hospitalized patients that the HOD test failed to differentiate between schizophrenics and neurotics, whereas a nursing observation of behavior scales did so. Still another study (38) by a psychiatrist who advocates the use of niacin in both neurotics and schizophrenics states, "As I used the HOD test more extensively, it was surprising to find that a number of neurotics and personality disorders had high perceptual scores and some had high total scores. These individuals did not appear to be schizophrenic or to be pseudoneurotic schizophrenics. . . . These individuals tended to be those who appeared as if they were almost constantly flooded with adrenalin and who showed such vaso-motor responses as sweaty palms, palpitations and tremor." Such patients, Dr. Ward reports, respond well to 3.0 g of NAA added to their other medication. The same author reports favorable results with five manic-depressives who showed "relative hypoglycemia" by using NAA and a high protein/low carbohydrate diet. It is interesting that this author finds

much greater "relative hypoglycemia" in neurotics than in schizophrenics. He also reports results on 49 schizophrenics and 34 non-schizophrenics. These data presented in two tables show that 87.8% of his schizophrenics were either improved or much improved and 88.2% of his non-schizophrenics were improved or much improved. In other words, almost precisely the same results were obtained in schizophrenics and non-schizophrenics given NAA and other unstated medications, using HOD criteria, clinical judgments and patient impressions.

It is unfortunate that neither the originators of the test, nor many other independent psychologists, have attempted to cross validate its reliability and validity. However, systematic scrutiny of the questions in the test by several experienced psychiatrists and psychologists yields the impression that it is far from specific for schizophrenia and that manics, depressives, and even many anxiety neurotics, might be diagnosed as schizophrenic by this test and that much additional data in the form of history, repeated clinical interview and other psychological tests would be required before a certain diagnosis could be made.

In 1963 Hoffer and Osmond (88) reported a new psychiatric illness called malvaria. The criterion for this illness was the finding
34 of a mauve colored spot obtained from the urine of some psychiatric patients after solvent extraction and chromatography. Examining the relationship between the mauve factor and symptoms, they observed that a diagnosis of schizophrenia could be independently made on most of the patients. Patients not diagnosed as schizophrenic but producing the mauve factor displayed some features characteristic of the schizophrenic syndrome. They were depressed, seclusive and overactive, had more readmissions and stayed longer in the hospital. This suggested that the diagnosis might well have been schizophrenia. The mauve factor was also said to correlate very highly with abnormal HOD scores, and at one point Hoffer suggested that all malvarians regardless of clinical diagnosis and HOD scores should be given the benefits of nicotinic acid treatment (89). Other workers, using Hoffer's chemical procedure, found the mauve factor to appear across diagnostic classes and in some normal adults and children (90). Craig (87) found the mauve spot in 12 of 19 schizophrenics and 13 of 19 neurotics.

Ellman et al. (91) found a highly positive though not perfect correlation between mauve production and the ingestion of phenothiazines. The mauve factor was identified by Irvine et al. (92) as 2,4 dimethyl-3-ethyl pyrrole, and this has been confirmed by Sohler et al. (93), who find it to have sedative properties when injected intravenously into rabbits. Although it was found in the urine of

two schizophrenic patients who were not on phenothiazines, it was found in the urine of only one out of six patients receiving phenothiazines and was not sought in the urine of normals. Furthermore, its mild sedative properties make it quite unlikely that it is an excitant or endogenous psychotogen.

Although the evidence suggests that both the mauve test as employed by Hoffer and the HOD test are not reliable for the diagnosis of schizophrenia, these are nonetheless used along with unspecified clinical criteria for the diagnosis of this illness, the initiation of treatment and the assessment of improvement.

In the megavitamin treatment program patients are divided into three graded categories based upon the severity of their symptoms and their response to graded forms of treatment. These are described in a treatment manual (18). They have been summarized by Hoffer (6) as follows.

> Phase I—This treatment is given to schizophrenic patients who are acute, cooperative, or have families who can cooperate for them and who do not require ECT. They are started on vitamin B-3, three grams per day. It is essential to use 500 or 1,000 milligram tablets since smaller tablets are too bulky and may produce a lot of anorexia. Patients are warned of the flush if nicotinic acid is to be used. The indications for either nicotinic acid or nicotinamide are given in a physicians treatment manual I have prepared [18]. Patients are also given ascorbic acid (3 grams per day) and may be given pyridoxine (¼ to ½ grams per day). They are advised on optimum nutrition, which means eliminating sucrose from their diet and encouraging them to have three meals per day. The restriction on sucrose forces them to utilize the more nutritious foods. I also advise them to discontinue the use of refined cereals and breads. If patients are very depressed or very agitated, they are given the usual antidepressants or tranquilizers in the usual dose ranges. A large number of early cases, especially during adolescence, do not require these psychoactive adjuncts, nor will they take them even when recommended. They do not like the intellectual dulling they produce. If one month later the patients are better they are maintained on the program until they are well. If progress is slow, the dose of vitamin B-3 is increased. The range for nicotinic acid is 3 to 30 grams per day. If the dose is too high the patients will experience nausea and vomiting. If this occurs, the medication is stopped for a couple of days. Then patients resume medication at a dose of 1 to 3 grams per day below the nauseant dose. When the patient is well, the antidepressant or tranquilizer is reduced slowly until the patient is maintained on vitamins only. The patient may require maintenance for life. After the patient has been well several years

there is no harm in going off of the medication as a test. However, at the first resurgence of symptoms, especially fatigue, depression or anxiety, the medication with vitamins must be resumed. There are other refinements of treatment which cannot be described here. They include attention to histamine blood levels; the presence of kryptopyrrole in the urine [92, 94], which increases the need for pyridoxine [95], and to the correction of trace elements and mineral metabolism. They will be described in the volume "Orthomolecular Psychiatry" edited by Dr. D. R. Hawkins and Dr. L. Pauling (in press) [96]. Practically all Phase I patients are outpatients.

Phase II—Patients who do not respond to Phase I treatment or who are too sick to be treated as outpatients or who are deeply depressed (suicidal) or very psychotic are classed as Phase II therapy patients. They are maintained on the same chemotherapeutic program and in addition are given a series of ECT. The megavitamins greatly reduce the usual confusion and memory loss generated by ECT. A series may run from 5 to 15; usually I use between 5 and 10. Patients who recover are maintained on the medication as are Phase I patients.

Phase III—Patients who do not respond to Phase II are classed as Phase III. This class also includes chronic schizophrenic patients such as are resident in mental hospitals or in modern times are resident in nursing homes, special care homes and foster homes. The new community psychiatry is dispersing chronic schizophrenics into the community, heavily tranquilized but not better. Perhaps they are worse off, for a bad mental hospital is better than a bad nursing home [96]. Phase III cases may require several series of ECT and several sessions in hospital. Usually each series of ECT produces a new level of improvement. (pp. 16-17).

Earlier Hoffer (18, 97, 98) employed a fourth category of treatment failures from Phase III. Such patients received penicillamine 2.0 grams per day concurrent with ECT for 10-20 days and might receive high doses of thyroid to set their pulse at 110-120, antidepressants in high doses, butyrophenones, thiamine 1.0-2.0 grams/day to reduce depression and 500 mg of pyridoxine/day. In 1967 Hoffer (18) advocated the use of ECT usually without anesthesia. It is not known whether this procedure is still recommended. In his most recent claim Hoffer (6) summarizes the results of orthomolecular psychiatry as follows.

[a] Acute schizophrenics—i.e., patients ill about a year or so, or who have had several attacks from which they have more or less recovered. I would expect over 90% to recover, to be well, provided that they are taken through the program de-

> scribed in this report over a two year period. The other 10% will be better, none will be worse.
>
> [b] Chronic schizophrenics who have been in the community, may have had many admissions but have not been damaged by many years of residence in a psychiatric institution. A five year orthomolecular program should see about 75% well and much improved.
>
> [c] Chronic schizophrenics resident many years in mental hospitals or in modern times heavily tranquilized in community mental health center sponsored homes. A very small proportion will never become well; the majority will be improved and none will have been made worse. (pp. 17-18).

It is impossible to determine the percentage of Hoffer's patients who fall into each of the three or four diagnostic and treatment phases which he employs. Nor, more importantly, does he anywhere offer data indicating the percentages of his clinical successes that fall into each category. This methodological omission is not without bearing on his outcome claims for if it should be the case that most of his "recoveries" in fact come from Phase I, one must seriously doubt that the patients were all truly schizophrenic. If they come from Phases II, III or IV, then it would seem plausible that the critical treatment variables may not be the specific vitamin combinations but rather the additional elements of the treatment regimen which he recommends for these latter diagnostic categories. Hoffer himself seems to believe this for in criticizing Ban's negative results he states (6): "The orthomolecular program was not followed: (1) the dose was fixed, too heavy for some and too low for others; (2) no ECT was used; (3) other vitamins were not used; (4) there was no dietary control. Even so, had they used ECT they would have corroborated our 1957 results. I have treated patients who received treatment by Ban's colleagues with no success who are now well, having received one or more series of ECT since leaving their unit." (p. 19).

From the foregoing it is clear that megavitamin therapy is not a single specific form of treatment, but part of a complex treatment program which has evolved over the years. This now includes anti-anxiety agents, major tranquilizers, penicillamine and hormones—all given as deemed necessary. Niacin therapy as advocated by Hoffer and Osmond is supposed to be aimed at the treatment of schizophrenia, but it is clear from the preceding considerations that they recommend treatment prior to the development of overt schizophrenia, based on abnormal urine tests and psychological test material, and "an awareness that schizophrenia is more prevalent than believed." It must be asked whether the assertion of such increased

prevalence is sufficient to support their argument, for they advance no epidemiologic studies to support this thesis. Such a belief in their capacity to predict schizophrenia is unsupported by any evidence, and may lead to the inclusion of patients who do not have and will not develop schizophrenia. These patients would certainly bias his results favorably.

The diagnostic criteria as stated by Hoffer in his monograph (18) also raise questions as to the fraction of the patients that they are treating successfully that actually have schizophrenia. This question is particularly pertinent to his Phase I, ambulatory, patients. He feels that the appearance of a classical thought disorder is symptomatic of chronicity, a position which we do not think would be shared by most psychiatrists. In addition, we think that most psychiatrists would be reluctant to diagnose schizophrenia without the presence of thought disorder. He seems to see the pseudoneurotic type of schizophrenia as defined by Hoch and Polatin as the paradigm for early schizophrenia which would seem to allow the inclusion of virtually all forms of neurosis as schizophrenia, if this diagnosis is not carefully used. In his article, "Borderline States" (78), Knight has reviewed the evidence which indicates that such patients may not be schizophrenic in the usual sense, and that the
 clinical course in such patients is one of a relatively stable instability, with little tendency to worsening to an overtly chronic schizophrenic state.

Hoffer's use of Conolly's definition (18) of psychosis would also seem to allow for the treatment of many other forms of psychotic illness as schizophrenia. The diagnosis is also seen to depend upon the presence of the mauve factor in the urine and a positive HOD test. Neither of these tests has demonstrable specificity, reliability or validity.

VI. QUANTITATIVE ASPECTS OF MEGAVITAMIN THERAPY, INCOMPATIBILTY OF METHYL-ACCEPTOR AND NAD POSITIONS, AND TOXICITY

Characteristic of megavitamin therapy are the massive doses of the vitamins required. To illustrate the magnitude of the difference between ordinary nutritional requirements and the doses employed for the treatment of schizophrenia, the estimated daily human requirement for NA is approximately 10-25 mg per day, depending on age and sex (99). In 1952, Hoffer and Osmond (11) began the use of NA in doses up to 5 g/day for the treatment of schizophrenia. Since then, quantities up to 20 g/day, or 750 times the average daily requirement, have been suggested (21). More recently, proposals have been made for the use of similarly large quantities of ascorbic acid and other members of the vitamin B complex. For example, ascorbic acid (average daily nutritional requirement 75-100 mg/day) has been used by megavitamin proponents in quantities ranging from 1 to 30 g/day; pyridoxine (2-3 mg/day average requirement), 50 to 500 mg/day; B_{12} (10-15 μg/day average requirement), 1-2 mg/day; thiamine (2.5 mg/day average requirement), 150 mg/day; folic acid (1-2 mg/day average requirement), 30 mg/day. Such massive dosages far exceed currently established vitamin dosages required to correct known metabolic deficiency syndromes in the average population.

Certain vitamin deficiency syndromes which respond quickly to massive doses of water soluble vitamins have been found to occur in children and have been described by Rosenberg (100) as vitamin dependency illnesses. These are very rare. Those which have been found show a Mendelian pattern of inheritance. They appear early in life; they are associated with the demonstrable presence of abnormal amino acids of their derivatives in the blood or urine and they demonstrate themselves in a variety of clinical syndromes ranging from anemia to convulsions and mental retardation. Typically there is a specific biochemical abnormality affecting only one of the many

protein apoenzymes which a specific vitamin functioning as a coenzyme catalyzes. Vitamin dependency illnesses have been reported for vitamins B_1, B_6, B_{12}, and folic acid. Except for Hartnup's disease, which is associated with poor intestinal absorption of tryptophan, no such illnesses have been found for nicotinic acid.

Megavitamin proponents would like to compare schizophrenia to these established vitamin dependency illnesses. They differ, however, in certain crucial regards. (1) There are no clear-cut, simple inheritance patterns in schizophrenia. (2) There are no well-established specific aminoacidopathies nor other metabolic disorders in schizophrenia. (3) There are no clear somatic manifestations of schizophrenia. (4) The therapeutic response to the appropriate vitamin is quick and dramatic in the dependency illnesses; this is not so for the vitamin response to schizophrenia. (5) The vitamin dependency illnesses are demonstrable in infancy or early childhood; this is not true for most schizophrenia.

The true vitamin dependency illnesses require exceptionally high daily doses of specific vitamins from birth throughout life. If these are not furnished, growth and normal development are affected. By contrast, in schizophrenia there is apparently an adequate vitamin intake for growth and development until the illness becomes manifest in the teens or early adult life. According to the proponents the vitamin requirements are then massively increased for life. No similar illnesses are established in other branches of medicine.

Whether or not the etiology of the schizophrenias and other severe forms of psychopathology in man, in certain individuals at least, also lies in either a genetic or an acquired metabolic vitamin dependency condition, as megavitamin proponents claim, is as yet unknown. If they do, they are unique in that the illness typically does not appear in infancy and has no well-established biochemical abnormalities.

Two points must be stressed in any consideration of the use of vitamins in massive doses. These are, first, that vitamins at such doses may have pharmacological actions independent of their role as vitamins; and second, that they are not necessarily devoid of toxicity. These points may be illustrated with particular reference to vitamin B_3.

The two theoretical bases adduced by megavitamin proponents for the effectiveness of NA therapy (nicotinic acid as a methyl acceptor and NAD deficiency) are in fact generally incompatible, because NAA, when functioning as a vitamin, is bound to the remainder of the coenzyme molecule by the nitrogen of its pyridine ring and hence can no longer accept methyl groups. Similarly, N-methyl nicotinamide cannot become a part of the NAD coenzyme.

A digression into nomenclature is perhaps in order at this point. By common definition a vitamin is not only an essential nutrient, but it is essential because it is transformed into a coenzyme vital for metabolic reactions. When nicotinic acid is functioning as a methyl acceptor, it is not a vitamin but rather a pharmacological agent administered in pharmacological doses. Vitamins in very large doses, it must be emphasized, have actions independent and different from their actions as coenzyme precursors. This is clearly shown by the following considerations. Both nicotinic acid and nicotinamide have identical vitamin B_3 action at equimolar doses. Yet at very high doses, nicotinic acid causes vasodilation and lowers blood cholesterol. At similar doses nicotinamide does neither. Furthermore, in measurements of acute toxicity, nicotinamide is eight times as toxic as nicotinic acid. Clearly, a vitamin in huge doses does not always function exclusively as a vitamin. The use of the term "megavitamin therapy" may therefore even be inappropriate under these special high dose conditions. Similarly, there may be nothing orthomolecular about the properties of NA but not NAA as a vasodilator.

Nicotinic acid and nicotinamide are both metabolized in large measure by methylation. The major metabolite appearing in the urine appears to be N′methylnicotinamide. The capacity to accept methyl groups and thus diminish the size of the methionine-supplied methyl pool is one of the possible mechanisms suggested for the effectiveness of nicotinic acid or the amide in the treatment of schizophrenia. In fact, however, nicotinic acid is not an especially good methyl acceptor and animal studies by Baldesserini (104) have shown that large doses of nicotinic acid fail to lower S-adenosyl methionine, the active form of methionine as a methyl donor. The capacity of NA and NAA to accept methyl groups is shared by ethanolamine, which when methylated forms choline, and by guanidoacetic acid, which yields creatine. Neither of these compounds is a vitamin and unfortunately neither has been tested clinically for anti-schizophrenic properties. L-DOPA, which in the large doses employed in Parkinsonism, is also a methyl acceptor, is not clinically effective in schizophrenia and may exacerbate symptoms. On the other hand, as noted above, NAD cannot function as a methyl acceptor because the nitrogen is already bound to the ribose moiety of the dinucleotide. As methyl acceptors, then, nicotinic acid and the amide are *not* functioning as vitamins, but rather as pharmacological agents whose properties may be desirable, but are independent of their fundamental role as vitamins. The semantics are confusing, but strictly speaking NA as a methyl acceptor is not a vitamin.

Essentially, then, the two views of NA as a vitamin precursor

of NAD and as a methyl acceptor are incompatible, except for the possibility that there is in schizophrenia double deficit—both a vitamin deficiency and a transmethylation defect and that nicotinic acid has the happy fortune to serve two purposes simultaneously.

Secondly, in view of the very high dosages of B_3 (and the other water-soluble vitamins) utilized by proponents of megavitamin therapy, it becomes a very necessary *medical* consideration to evaluate carefully the possibilities of and evidence regarding the toxicity of these substances when used in such massive dosages, which, furthermore, are more often than not prolonged over long periods of time—in some cases indefinitely. It is even more necessary when huge doses are recommended during pregnancy and when 1.0 g daily is recommended in the diets of all children.

The statements of megavitamin proponents on this issue are, however, unfortunately vague and occasionally flatly contradictory. Thus, Hoffer (1965), in a Xeroxed broadside for distribution in response to personal inquiries from physicians and private (lay) citizens, unequivocally and unqualifiedly states under his heading "Dangers": "There are none. These vitamin chemicals are safer than aspirin." And in another paper, Hoffer and Osmond (24) say: "nicotinic acid is remarkably safe. . . . In over 400 cases in Saskatchewan, we have seen no cases or (sic) toxicity." (p. 80). Additional statements to this effect include: "When a medication as free of toxicity as nicotinic acid can produce such a marked improvement in recovery of schizophrenic patients, there can be no valid reason for depriving these patients of bettering their chances of recovery" (19, p. 240); niacin is inexpensive and safe, and "among least toxic of all medication used in psychiatry" (101, p. 163).

Elsewhere these writers are somewhat more guarded and ambiguous. Hoffer, for example, in his 1967 pamphlet (18) and in his 1971 paper (13) cites violent vasodilation with concomitant flushing (NA only), severe headache, nausea and other gastro-intestinal disturbances, bullous dermatitis, "In a couple of cases a shock-like reaction . . . with a drop in blood pressure" (18, p. 13), allergic reactions, possible liver damage, decreases in glucose tolerance and increases in blood uric acid levels. This rather impressive array of adverse reactions, however, is more or less written off by Hoffer as in each case (a) easily controlled by additional specific antagonist medication, (b) highly infrequent and/or idiosyncratic, (c) the list notwithstanding, NA and NAA are still "safer" than most other drugs currently used in psychiatry. The gastrointestinal symptoms are attributed to the inert filler used in preparation of the B_3 tablets. Most surprising of all, however, is Hoffer's claim in this same paper —in flat contradiction to his earlier statements cited above—that he

had *never* stated that B_3 was non-toxic. "This," he says, "obviously would have been a foolhardy and erroneous claim." (13, p. 499).

Another paper, frequently cited by megavitamin proponents as among their successes, adds to this list of toxic reactions. Lino Chinaglia (48), working in an Italian state hospital near Trent, found that of 14 acute schizophrenics treated with NAA in conjunction with ECT and chemotherapy, 5 had to have the amide discontinued because of severe adverse reactions, including intractable arterial hypotension, acute gastrointestinal disturbance, and/or severe psychomotor disturbance with hyperkinesia, delirium and hallucinations. Curiously, Chinaglia does not count these 5 patients as treatment failures.

As indicated above, however, disturbing as these immediate adverse reactions may be, the truly important question arising from the prolonged megadosage administration of B_3 is that of possible long-range toxicity. This issue has been carefully examined and comprehensively reviewed by Loren Mosher (102). While finding that B_3 does appear to be "relatively harmless," the available evidence seems to indicate that far more caution should be exercised in its long-term administration than the megavitamin proponents seem to recognize. Most of the work done on this issue has dealt exclusively with NA, but as it is known that NAA is far more toxic than the acid, the amide should be viewed with even more caution. The following is condensed from Mosher (102).

Animal studies have yielded inconclusive results—but with sufficient evidence *for* severe toxicity to warrant caution. Fatty livers have been reported in rats, and in dogs toxic effects such as bloody feces, convulsions, gastrointestinal erosions and petechiae, CNS lesions (shrunken, deeply stained cells in cortex, hippocampus and basal ganglia), albuminuria and glycosuria. More disturbingly, there is some, though as yet wholly inconclusive, evidence from studies with fowl that high-level dosages of NAA may have teratogenic effects.

Studies in man stem mainly from the long-term clinical use of NA as a blood cholesterol-lowering agent in the treatment of atherosclerosis. Toxic reaction findings are grouped by Mosher under the following headings:

Dermatological: the initial flush upon ingestion of NA has been found not to subside (as claimed by Hoffer) but to become chronic in 30 to 59% of patients. Figures for chronic pruritis are comparable. Rare cases of hyperpigmentation and acanthosis nigricans have been reported.

Gastrointestinal: 2 studies have shown incidence of duodenal ulcer (9/68 and 2/48) after sustained (96-130 wks) NA administra-

tional in dosages comparable to those utilized by megavitamin proponents (3-7.5 grams).

Hepatic: Reports of abnormal liver function vary from none to 45%. Symptomatology includes jaundice, hepatic dysfunction and intrahepatic cholestasis.

Carbohydrate metabolism: Hyperglycemia has been reported in 50 to 66% of non-diabetics taking NA. A study of six diabetic patients given 1-3 gm/day NA for 5-6 months showed that all six developed increased glycemia, glycosuria, free fatty acids and ketone bodies. Abnormal glucose tolerances have been reported.

Uric acid: Extraordinary increases of serum uric acid have been reported in two studies (62% and 72%, respectively). One of these studies included two cases of acute gouty arthritis.

Miscellaneous: One study reports a 10% incidence of heightened "nervousness," two panic states and one case of hypothyroidism. Another study reported the precipitation of incipient psychosis by NA.

The fact that most of these symptoms disappear upon discontinuance of NA administration offers little support to the megavitamin therapy rationale, as its proponents consistently emphasize that many "schizophrenics" may require extremely long-term periods of B_3 therapy—some, indeed, for life. In view of the possible severely toxic consequences of sustained administration of megadosages of B_3, and in view of the paucity of present evidence indicating a conclusive answer either pro or contra on this question, it certainly cannot be responsibly maintained without qualification that B_3 in megadosages is a "completely safe" pharmacological agent. This consideration acquires even more weight in light of the fact that its therapeutic efficacy in the treatment of schizophrenia is very dubious.

VII. CONCLUSIONS

The preceding material should make it clear that in our view the results and claims of the advocates of megavitamin therapy have not been confirmed by several groups of psychiatrists and psychologists experienced in psychopharmacological research. The negative results have been obtained with adequately sized populations, employing careful observations by physicians, psychologists and nurses and employing standardized, reliable psychological and behavioral rating scales and appropriate statistics. They have been designed to test the efficacy of vitamin B_3 (nicotinic acid, nicotinamide, niacin) and the coenzyme derived from it (nicotinamide-adenine-dinucleotide), and this has been found to be useless and not without hazard. Thus, the claims of the megavitamin proponents made as far back as 1957 have not been confirmed.

The theoretical basis for megavitamin treatment especially with nicotinic acid has been examined and found wanting. The chemical and psychological tests employed for diagnosis and treatment response have been examined and found lacking in both reliability and specificity. It is suspect that a substantial number of ambulatory patients (Phase I) for whom the best results are obtained may not actually have been schizophrenic and represent a group for whom spontaneous recovery is high.

Since 1957 and particularly since 1968 the treatment methods and theoretical basis for megavitamin therapy have changed. Such practitioners now call themselves orthomolecular psychiatrists and employ additional vitamins in doses very much larger than the average estimated nutritional requirements, as well as ECT, conventional major and minor tranquilizers, and antidepressants. They also employ special diets, hormones and other medication. Since the original studies reported in 1957 they have performed no controlled double-blind studies and since the early 1960's they have not reported new data in the major psychiatric or scientific literature. Instead, they have relied upon anecdotal data with claims that they have treated many thousands of patients and that 90% of acute schizophrenics become well within two years of treatment, and that a 5-year treatment program will see about 75% of both acute and chronic schizophrenics well or much improved. Such claims have been broadly

distributed in popular books, the lay press and a journal published by the society in which they have organized.

It has thus far not been possible to replicate precisely the treatment program now advocated by the orthomolecular psychiatrists, especially for Phases II and III patients, because the procedures change from year to year and because of the number of variables which enter into the treatment of each patient. Thus, each patient may receive as many as six vitamins in large doses individually determined by the treating physician as well as other psychotropic drugs and hormones whose doses are also individually determined for each patient. Electroconvulsive therapy, specifically advocated for hospitalized patients (Phases II and III patients), has especially not been replicated because it has generally fallen out of favor for the treatment of schizophrenia since the advent of the phenothiazines and butyrophenones.

Since most of the tests showing no value of nicotinic acid have dealt with Phases II and III patients and precise replication has not been carried out, it is barely possible that some of the other aspects of the treatment program (e.g., the ECT) may be the crucial variables in failing to confirm the positive results. If this should prove to be the case, then ECT may again deserve a place in the conventional

treatment of schizophrenia. But if it is the case, then megavitamin or orthomolecular treatment is a misnomer, for ECT is certainly neither. It is also possible that other water-soluble vitamins will prove to be more effective than NA. Nonetheless, the massive use of niacin has always been the cornerstone of the theory and practice of megavitamin advocates. Since this has proved to have no value when it is employed as the sole variable along with conventional treatments of schizophrenia, the burden of proof for the complex and highly individualized programs now advocated would appear to be on the proponents of such treatment.

None of the above is meant to imply in any way that a biological defect may not exist in some of the schizophrenias and that better forms of prevention and treatment may not some day be found. Indeed a search for biological defects is actively underway in many laboratories and is supported at an annual level of $10,000,000 by the National Institute of Mental Health. A recent summary of the strategies, hypotheses and experiments underway throughout the world has been published by Kety and Matthysse (3).

We have carefully reviewed the literature and existing case reports concerning megavitamin therapy. We have seen innumerable reports in the lay press attesting to its efficacy not only in schizophrenia but also alcoholism, drug abuse and aging. Some of us have referred patients who have wanted this type of treatment to ortho-

molecular psychiatrists and have found that the highly advertised low cost of treatment is far from low when hospitalization is indicated as it frequently is. We have also encountered treatment failures who appear in our clinics. These must be balanced with occasional anecdotal reports which we have heard from relatives and friends of patients who are reported to have responded favorably to megavitamin therapy after years of failure with conventional treatment.

We are left with a sense of puzzlement as to why the results of serious and major attempts to demonstrate the value of nicotinic acid have been so uniformly negative in the hands of independent investigators. Not only have no statistical differences been found, but the possibility of a small subgroup that is responsive in a large heterogeneous group of schizophrenics appears to be minimal because no dramatic individual recoveries have been reported in these studies. If such a subgroup exists, it would consist of those patients with good premorbid interpersonal history such as those found by Wittenborn (105) in a retrospective study. Wittenborn questions the aptness of the term "schizophrenic" for such patients. We are also puzzled by the reports of the megavitamin advocates that they are able to convert many conventional treatment failures into success by their procedures. It remains possible that the enthusiasm, dedication and personal investment of the megavitamin therapists may contribute to the well-being of the patients. While this may be the case, it would be helpful if physicians independent of the orthomolecular group would report to the APA their positive experiences with patients whom they have referred for orthomolecular treatment. It would be equally useful if they would report cases which have come to them after failure on megavitamin treatment by orthomolecular psychiatrists.

We regret this conclusion because some good may have come out of this method of treatment. Guilt and shame have probably been reduced in both patients and their families because a metabolic disease is somehow easier to bear than a psychogenic illness. The establishment of self-help groups like Schizophrenics Anonymous is a desirable spin-off. The organization of a community mental health center with group therapy, a day care center, halfway house and job placement which is held together by orthomolecular concepts may be useful (96). Countering this, of course, is the nagging question of how many people have been diagnosed as schizophrenic and treated successfully by orthomolecular means when they may not have been schizophrenic at all. We are also troubled by the question of the consequences of the destruction of mental health programs like that of the Retail Clerks International in Los Angeles by megavitamin proponents and the creation of new orthomolecular clinics, like that

recently reported in San Bernardino, that may not offer the scope of services given by the more conventional clinics.

Socially desirable outcomes have sometimes been derived from myths or fervently held beliefs. To this extent the orthomolecular movement in psychiatry may be socially useful. But if psychiatry is to become and remain scientific, it must meet the test of scientific validity. Nicotinic acid therapy does not do so at this time. If there is to be wide professional acceptance of a megavitamin or orthomolecular treatment program, it must be based upon demonstrable biochemical defects in this condition and upon adequately designed and carefully executed clinical experiments with data presented to the scientific and professional community in an acceptable fashion. Such publications have not appeared from proponents of the orthomolecular approach for many years.

In the end the credibility of the megavitamin proponents and the orthomolecular psychiatrists becomes the crucial issue because it is never possible to fully prove or disprove a therapeutic procedure. Rather the theory and practice gain or lose credibility as its premises, methods, and results are examined, and attempts are made at clinical replication by independent investigators. This review and critique has carefully examined the literature produced by mega-
18 vitamin proponents and by those who have attempted to replicate their basic and clinical work. It concludes that in this regard the credibility of the megavitamin proponents is low.

Their credibility is further diminished by a consistent refusal over the past decade to perform controlled experiments and to report their new results in a scientifically acceptable fashion.

Under these circumstances this Task Force considers the massive publicity which they promulgate via radio, the lay press and popular books, using catch phrases which are really misnomers like "megavitamin therapy" and "orthomolecular treatment," to be deplorable.

REFERENCES

1. Hoffer A, Osmond H and Smythies J: Schizophrenia: a new approach. II. Result of a year's research. J Ment Sci 100:29-54, 1954
2. Rosenthal D and Kety SS (Eds): The Transmission of Schizophrenia. New York, Pergamon Press, 1968
3. Kety SS and Matthysse S (Eds): Prospects for Research on Schizophrenia: A Report Based on an NRP Work Session. Neurosci Res Prog Bull 10:370-507, 1972
4. May PRA: Treatment of Schizophrenia. New York, Science House, 1968
5. Grinspoon L, Ewalt JR and Shader RI: Schizophrenia: Pharmacotherapy and Psychotherapy. Baltimore, Williams and Wilkins Co., 1972
6. Hoffer A: Orthomolecular treatment for schizophrenia. Med Counterpoint 4:10, 1972
7. Hoffer A, Osmond H and Smythies J: Schizophrenia: a new approach. II. Results of a years' research. J Ment Sci 100:29-54, 1954
8. Hoffer A: Pellagra and schizophrenia. Psychosom 11:522-525, 1970
9. Pauling L: Orthomolecular psychiatry. Science 160: 265-271, 1968
10. Hawkins DR, Bortin AW and Runyon RP: Orthomolecular psychiatry: niacin and megavitamin therapy. Psychosom 11:517-521, 1970
11. Hoffer A, Osmond H, Callbeck MJ, et al: Treatment of schizophrenia with nicotinic acid and nicotinamide. J Clin Exp Psychopath 18:131-158, 1957
12. Hoffer A: Vitamin B_3 dependent child. Schiz 3:107-113, 1971
13. Hoffer A: Megavitamin B-3 therapy for schizophrenia. Can Psychiat Assoc J 16:499-504, 1971
14. Hoffer A and Osmond H: Treatment of schizophrenia with nicotinic acid: a ten year follow-up. Acta Psychiat Scand 40:171-189, 1964
15. Denson R: Nicotinamide in the treatment of schizophrenia. Dis Nerv Syst 23:167-172, 1962
16. Cott A: Treating schizophrenic children. Schiz 1:44-49, 1969
17. Cott A: Orthomolecular approach to the treatment of learning disabilities. Schiz 3:95-105, 1971
18. Hoffer A: A Program for Treating Schizophrenia and Other Conditions Using Megavitamin Therapy. Saskatoon, Modern Press, 1967
19. Hoffer A: The effect of nicotinic acid on the frequency and duration of re-hospitalization of schizophrenic patients: a controlled comparison study. Int J Neuropsychiat 2:234-240, 1966

20. Hoffer A: Niacin Therapy in Psychiatry. Springfield, Illinois, C. C. Thomas, 1962
21. Hoffer A: Comparison of xanthine nicotinate and nicotinic acid as treatment for schizophrenia. Schiz 1:24-37, 1969
22. Osmond H: Background to the niacin treatment. J Schiz 1:125, 1967
23. Wittenborn JR: Niacin in the treatment of schizophrenia. Interim report, April 1, 1972 (unpublished)
24. Hoffer A and Osmond H: Nicotinamide adenine dinucleotide (NAD) as a treatment for schizophrenia. J Psychopharm 1:79-95, 1966
25. Cannon WB: Bodily Changes in Pain, Hunger, Fear and Rage. New York, R. Appleton and Co., 1915
26. Osmond H and Smythies J: Schizophrenia: a new approach. J Ment Sci 98:309, 1952
27. Noteboom L: Experimental catatonia by means of derivatives of mescaline and adrenalin. Proc N Y Acad Sci 37:562-574, 1934
28. de Jong H: Experimental Catatonia. Baltimore, The Williams and Wilkins Company, 1945
29. Hoffer A: Adrenochrome in blood plasma. Amer J Psychiat 114:752-753, 1958
30. Hoffer A: The adrenochrome theory of schizophrenia: a review. Dis Nerv Syst 25:173-178, 1964
31. Green D E and Richter D: Adrenalin and adrenochrome. Biochem J 31:596-616, 1937
32. Osmond H and Hoffer A: Massive niacin treatment in schizophrenia: review of a nine-year study. The Lancet 1:316-319, 1962.
33. Beebe W E: Schizophrenia and nicotinic acid. Brunswick Hospital Center Conference on the Concepts and Treatment of Schizophrenia. January 21-22, 1967
34. Cott A: Treatment of ambulant schizophrenics with vitamin B_3 and relative hypoglycemic diet. J Schiz 1:189-196, 1967
35. Cott A: The parenthal use of vitamins in the treatment of schizophrenia. Schiz 2:177-179, 1970
36. Galambos M: Use of nicotinic acid for treatment of some adult mentally retarded patients. Brunswick Hospital Center Conference on the Concepts and Treatment of Schizophrenia, January 21-22, 1967
37. Hawkins DR: Practical application of the results of biochemical research in everyday clinical practice. Brunswick Hospital Center Conference on the Concepts and Treatment of Schizophrenia, January 21-22, 1967
38. Ward JL: Treatment of neurotics and schizophrenics using clinical and HOD criteria. J Schiz 1:140, 1967
39. Tobin JM: Treatment of schizophrenia with nicotinic acid, an overview. J Schiz 1:182, 1967
40. Robie T: Treatment of schizophrenia. Brunswick Hospital Conference on the Concepts and Treatment of Schizophrenia, January 21-22, 1967

41. Kline NS, Barclay GL, Esser AH, et al: Diphosphopyridine nucleotide in the treatment of schizophrenia. JAMA 200:177-178, 1967
42. Gallant DM, Bishop M and Steele CA: DPN (NAD-oxidized form): a preliminary evaluation in chronic schizophrenic patients. Curr Ther Res 8:542-548, 1966
43. Kline NS, Barclay GL, Cole JO, et al: Controlled evaluation of nicotinamide adenine dinucleotide in the treatment of chronic schizophrenic patients. Brit J Psychiat 113:731-742, 1967
44. Gottlieb J: Personal communication
45. Meltzer H, Shader R and Grinspoon L: The behavioral effects of nicotinamide adenine dinucleotide in chronic schizophrenia. Psychopharmacologia (Berl) 15:144-152, 1969
46. Saarma J and Vasar H: Nicotinic acid as an adjuvant in the treatment of chronic schizophrenic patients with special reference to changes in higher nervous activity. Curr Therap Res 12:729-733, 1970
47. O'Reilly PO: Nicotinic acid therapy and the chronic schizophrenic. Dis Nerv Syst 16:67-72, 1955
48. Chinaglia L: Sul trattamento della schizofrenia con amide nicotinica. Fol Psychiat 8:123-130, 1965
49. Ashby WR, Collins GH and Bassett M: The effects of nicotinamide and placebo on the chronic schizophrenic. J Ment Sci 106:1555-1559, 1960
50. Greenbaum GHC: An evaluation of niacinamide in the treatment of childhood schizophrenia. Amer J Psychiat 127:129-132, 1970
51. McGrath SD, O'Brien PF, Power PJ et al: Nicotinamide treatment of schizophrenia. Schiz Bull 5:74-76, 1972
52. Wittenborn JR, Weber ESP and Brown M: Niacin in the long-term treatment of schizophrenia. Arch Gen Psychiat 28:308-315, 1973
53. Ramsay RA, Ban TA, Lehmann HE, et al: Nicotinic acid as adjuvant therapy in newly-admitted schizophrenic patients. Can Med Assoc J 102:939, 1970
54. Ananth JV, Ban TA, Lehmann HE, et al: Nicotinic acid in the prevention and treatment of methionine-induced exacerbation of psychopathology in schizophrenics. Can Psychiat Assoc J 15:15, 1970
55. Ban TA and Lehmann HE: Nicotinic Acid in the Treatment of Schizophrenias. Can Ment Health Assoc Collab Study. Toronto, Can Ment Health Assoc, 1970
56. Ban TA: Nicotinic acid in the treatment of schizophrenia. Complementary Report A. Toronto, Canadian Mental Health Association, 1971
57. Ban TA: Nicotinic acid and psychiatry. Can Psychiat Assoc J 16: 413-431, 1971
58. Ananth JW, Vacaflor L, Kelhwa G et al: Nicotinic acid in the treatment of newly admitted schizophrenic patients: A placebo-controlled study. Int J Clin Pharmacol 5:406-410, 1972

59. Ban TA and Lehmann HE: Niacin in the treatment of schizophrenias: alone and in combination. Presented at the VIIIth C.I.N.P. Congress, Copenhagen, August 14-17, 1972
60. Elvehjem CA, Madden RJ, Strong FM, et al: The isolation and identification of the anti-black tongue factor. J Biol Chem 123:137-149, 1938
61. Fouts PJ, Helmer OM, Leplovsky S, et al: The treatment of human pellagra with nicotinic acid. Proc Soc Exp Biol Med 37:405-407, 1937
62. Smith DT, Ruffin JM and Smith SG: Pellagra successfully treated with nicotinic acid: a case report. JAMA 109:2054-2055, 1937
63. Spies TD, Cooper C and Blankenhorn MA: Use of nicotinic acid in treatment of pellagra. JAMA 110:622-627, 1938
64. Lehmann HE: Post-traumatic confusional state treated with massive doses of nicotinic acid. Can Med Assoc J 51:558, 1944
65. Medlicott RW: Nicotinic acid in treatment of some psychiatric syndromes. New Zea Med J 44:28-33, 1945
66. Joliffe N, Bowman KM, Rosenblum LA, et al: Nicotinic acid deficiency encephalopathy. JAMA 114:307-312, 1940
67. Gregory I: The role of nicotinic acid (Niacin) in mental health and disease. J Ment Sci 101:85-109, 1955
68. Major RH: Classic Descriptions of Disease. Springfield, Ill, C. C. Thomas, 3rd ed, 1945
69. Henderson DK and Gillespie RD: A Textbook of Psychiatry for Students and Practitioners. London, New York, Oxford University Press, 1946
70. Brain WR: Diseases of the Nervous System. London, Oxford University Press, 4th ed, 1951
71. Sydenstricker VP: The clinical manifestations of nicotinic acid and riboflavin deficiency (pellagra). Ann Int Med 14:1499-1517, 1941
72. Sydenstricker VP and Cleckley HM: The effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. Amer J Psychiat 98:83-92, 1941
73. Axelrod AE, Gordon ES and Elvehjem CA: The relationship of the dietary intake of nicotinic acid to the coenzyme I content of blood. Amer J Med Sci 199:697-705, 1940
74. Schou M: Experiences with the fluorometric method for determination of the pyridine nucleotides in blood, with some determinations on blood from psychiatric patients. Biochim Biophys Acta 4:422-426, 1950
75. Detré TP and Jarecke HG: Modern Psychiatric Treatment. Philadelphia, J. B. Lippincott and Co, 1971
76. Bleuler E: Dementia Praecox oder Gruppe der Schizophrenien. Leipzig, Deuticke, 1911
77. Hoch PH and Polatin P: Pseudoneurotic forms of schizophrenia. Psych Quart 23:248, 1949
78. Knight RE: Borderline states. Bull Menninger Clin 17:1, 1953
79. Bleuler M: Remission of schizophrenia after shock therapy. Ges Neurol Psychiat 173:553, 1941

80. Klein DF and Davis JM: Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Williams and Wilkins, 1969
81. Cole JO: Phenothiazine treatment in acute schizophrenia. Arch Gen Psychiat 10:246, 1964
82. NIMH-PSC Collaborative Study Group: Clinical Effects of Three Phenothiazines in Acute Schizophrenia. Pub Rep #6, Bethesda, Md, USPHS, April 1966
83. Casey JF, Lasky JJ, Klett CJ, et al: Treatment of schizophrenic reactions with phenothiazine derivatives: a comparative study of chlorpromazine, trifluprομazine, mepazine, prochlorperazine, perphenazine and phenobarbital. Amer J Psychiat 117:97-105, 1960
84. Hoffer A and Osmond H: A card sorting test helpful in making psychiatric diagnosis. J Neuropsychiat 2:306-330, 1961
85. 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. 2. New York, Academic Press, 1967
86. Stewart CN and Mahood MC: A multiple group comparison of scores on the HOD. Can Psychiat Assoc J 8:133, 1963
87. Craig WJ: Biochemical schizophrenia: An investigation of "malvaria" and the HOD test using behavioral measures. Unpublished results, 1971
88. Hoffer A and Osmond H: Malvaria: a new psychiatric disease. Acta Psychiat Scand 39:335-366, 1963
89. Hoffer A: Quantification of malvaria. Int J Neuropsychiat 2:559, 1966
90. O'Reilly PO, Ernest M and Hughes G: The incidence of malvaria. Brit J Psychiat 111:741-744, 1965
91. Ellman GL, Jones RT and Rycert RC: Mauve spot and schizophrenia. Amer J Psychiat 125:849-851, 1968
92. Irvine DG, Bayne W, Miyashita H, et al: Identification of kryptopyrrole in human urine and its relation to psychosis. Nature 224: 811-813, 1969
93. Sohler A, Beck R and Noval JJ: Mauve factor re-identified as 2,4-dimethyl-3-ethylpyrrole and its sedative effect on the CNS. Nature 228:1318-1320, 1970
94. Hoffer A and Osmond H: The relationship between an unknown factor (US) in urine of subjects and HOD test results. J Neuropsychiat 2:363-368, 1961
95. Pfeiffer C: Personal communication to A. Hoffer, 1972
96. Funderburg R: Where Have All the Patients Gone? A California State Employees Association Report, 1972
97. Hoffer A: Manual for Treating Schizophrenia and Other Conditions Using Megavitamin Therapy. 1201 C.N. Towers, Saskatoon, Saskatchewan, 1970
98. Hoffer A and Osmond H: Some schizophrenic recoveries. Dis Nerv Syst 23:204-210, 1962
99. Quoted in Beeson PB and McDermott W (Eds): Cecil-Loeb Textbook of Medicine. Philadelphia, Saunders, 13th edition, 1971

100. Rosenberg LE: Vitamin-dependent genetic disease. Hosp Prac 5: 59-66, 1970
101. Hoffer A and Osmond H: Vitamin B_3 and krebiozen—a polemic. Schiz 2:161-165, 1970
102. Mosher L.: Nicotinic acid side effects and toxicity: a review. Amer J Psychiat 126:1290-1296, 1970
103. Bann T A: Psychopharmacology. Baltimore, Williams and Wilkins, 1969
104. Baldesserini RJ: Factors influencing S-adenosyl methionine levels in tissue. In Himwich HE, Kety SS and Smythies JR (Eds): Amines and Schizophrenia. New York, Pergamon Press, 1967
105. Wittenborn JR: Personal communication, 1973