MEGAVITAMIN THERAPY

In Reply To

THE AMERICAN PSYCHIATRIC ASSOCIATION TASK FORCE REPORT ON MEGAVITAMIN AND ORTHOMOLECULAR THERAPY IN PSYCHIATRY

Canadian Schizophrenia Foundation  August 1976
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This is the second report published by the Canadian Schizophrenia Foundation to give wider dissemination to its members and to members of similar organizations in the USA of corrections to the findings of the American Psychiatric Association Task Force Report #7, Megavitamin and Orthomolecular Therapy in Psychiatry.

The findings, opinions, and conclusions of these reports do not necessarily represent the views of the officers, members of the board, or all members of the Foundation. Each report does represent the thoughtful judgment and consensus of Dr. A. Hoffer and Dr. H. Osmond who prepared it, and it is considered a useful and substantive contribution to the ongoing analysis and evaluation of problems, programs, issues, and practices in a given area of concern: orthomolecular psychiatry.

A. Hoffer, M.D., Ph.D., F.A.O.P., F.R.S.C.(C)
President Canadian Schizophrenia Foundation
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In Reply to the American Psychiatric Association Task Force Report on
Megavitamins and Orthomolecular Psychiatry

A Hoffer, PhD, MD, F AO P, R C P(C)
H Osmond, MB, MRCP, FRCPsych

Canadian Schizophrenia Foundation
2135 Albert Street
Regina, Saskatchewan
S4P 2V1

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We decided to answer the American Psychiatric Association Task Force Report on Megavitamins and Orthomolecular Psychiatry with some reluctance since this kind of controversy is tedious and not really productive—there are many other things to do connected with the well-being of schizophrenic patients which should have higher priority than answering the criticisms of a committee none of whose members appear to have had direct clinical charge of a single schizophrenic patient treated by orthomolecular psychiatric therapy.

However, colleagues have pointed out to us that we had a special responsibility for replying to these critics, and if we failed to do so it would be assumed that our default indicated that we accepted some or perhaps most of their criticisms. Our reluctance as we shall note later on has been much more on account of the multitude of errors than upon the high quality of the criticisms. There is much to be gained from the observations and even strictures of an intelligent, fair critic. We are not so conceited or so provincial as to deny that, especially with the benefit of hindsight, experiments might have been done differently and papers discussing and describing our studies might have been differently written. However, having completed our critical study of our critics we feel that it has been worth the effort and hope that our readers will agree.

As far as the Task Force members are concerned we would remind them of Bernard Shaw’s aphorisms: “If you would injure your neighbor—better not do it by halves”.

Since the report was clearly intended to injure us it was doubly botched because, according to the American Psychiatric Association, it was supposedly a fair inquiry and as such it was a failure from the start. The moment that we doubted the impartiality of the chairman and committee members (presumably selected by him) it ceased to be an unbiased inquiry. The APA’s duty was to ask us whom we would consider to be unbiased among their 25,000 members or so, or how undue bias, one way or another, could be assured against. Their arbitrary assumption that they knew best is far more serious than the errors of Lipton, Mosher, Ban, et al.

That four-fifths of the committee came from two institutions and that the other member was a rival experimenter indicated ineptitude and insensitivity.
an examination of
the american psychiatric association
task force report
"megavitamins and orthomolecular
therapy in psychiatry"
american psychiatric association, 1973

The Task Force

This report begins by stating that "we shall examine carefully and critically the claims, the supporting evidence, the theoretical basis and the contrary evidence in detail." It is wholly proper for a professional association to study a new treatment in this way. The report ends with these words, "this review and critique has carefully examined the literature produced by megavitamin 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." The value that one attaches to the Task Force conclusions depends largely upon the intelligence, zeal, honesty, and detachment with which its members approached the objective which they had set for themselves. In this paper, we shall examine the composition of the Task Force, the nature of its report, and the manner in which it set out to examine megavitamin and orthomolecular therapy in psychiatry.

To attain their stated objectives, a lack of bias and prejudice was essential. It may surprise those who believe that the American Psychiatric Association would never allow its name to be attached to a document which did not meet these criteria to learn that three years before this report was published the chairman of that Task Force was conducting himself in a manner which did not suggest impartiality. Indeed, his behavior indicated to many who heard him speak that he had already made up his mind and was not inclined to change it.

At a public meeting in California arranged by Mr. Joe Desilva of Local 770 in Los Angeles, Dr. Morris Lipton read a paper on the theoretical aspects of megavitamin therapy and touched briefly on treatment. At this time none of the Ban-Lehmann studies had been reported and Wittenborn's work was still in progress. Nevertheless, Dr. Lipton's conclusions, which he expressed then, closely resembled what was published later by the committee of which he was chairman.
We are not the first to have questioned the propriety of using this report as a source of information. Linus Pauling, 1974, wrote: "The APA Task Force Report, 'Megavitamin and Orthomolecular Therapy in Psychiatry,' discuses vitamins in a very limited way (niacin only) and deals with only one of two aspects of the theory. Its arguments are in part faulty and its conclusions are unjustified." Hoffer, 1974, following a long and detailed examination, commented: "It is a mistake to use it as a reference source in evaluating megavitamin therapy because it is a mine of misinformation." These remarks may disappoint those who had supposed that the APA would provide a useful and reliable document, but they are less unexpected when one studies both the composition of the committee and its modus operandi.

When a committee is formed to report on a controversial issue, one assumes that the matter is important enough to warrant a careful, scholarly, and detached examination. The APA Council on Research and Development was correct in appointing a Task Force to examine megavitamin therapy for this was a matter of interest, concern, and discussion among both psychiatrists and the public. However, the Council erred gravely in failing to instruct the subcommittee, chaired by Dr. M Lipton, that not only must the committee be fair and objective, but they must also appear to be so.

A committee can appear to be fair even when they are not truly so by using two procedures either alone or together.

First: It may include among its members those who have had direct personal experience with the new treatment. These knowledgeable members of the committee can examine the data, question witnesses in an intelligent manner, and, finally, explain, reason, and argue with other members of the committee. It is with this in mind that in democracies government committees always include members of the major political parties. One-party committees, however admirable their members may be, are always suspect. If a minority of members believe that a report is incorrect or unfair they can then register an official dissenting view which is published with the majority opinion. The presence of members experienced with the treatment under review means that those appearing before the committee know that they will be questioned by any one of its members. This deters people from presenting mere hearsay evidence or opinions which cannot be backed with personal experience.

Second: Proponents of opposing views may be allowed to cross-examine each other. This is a procedure which was eventually done in the prolonged and controversial FDA vitamin hearings held in Washington recently. Dr. Miles Robinson, M.D., asked to be allowed to cross-examine some of the witnesses appearing before the hearing examiner. This right was at first denied him, but Dr. Robinson took the matter to court. The examiner was then rebuked and ordered to re-open the hearings to allow the cross-examination. The United States Court believed that a public inquiry should make every effort to determine the truth and decided that cross-examination, which had been denied earlier, would further this process. Either of these approaches alone increases the chances of objectivity, but to have even an appearance of fairness and so warrant public and professional confidence, both should have been employed.

In fact, neither was used. Consequently the committee appears to have been biased, and as we shall show, this appearance is not misleading. No provision was made to ask any physician experienced in the use of megavitamin therapy to appear before it, even though there were plenty available and willing to do so. Yet it has been reported that sessions were held in which members Of

Lord Devlin, a former British Law Lord (roughly the equivalent of a Supreme Court Justice in the U.S.A.), was quoted in the London Times, June 26, 1975, as saying in his Charley Lecture that "a judge's most important qualities were impartiality and second, the appearance of impartiality."
the committee consulted other psychiatrists and sought their views, even though they had never published any data on megavitamin treatment.

An official or legal body which conducted its affairs in such a manner would be promptly discredited. The APA's posture is the more questionable since it has always been very strong for constitutional and personal freedom and frequently advocates the humane and sensitive conduct of governmental and social affairs. Perhaps the APA has forgotten that charity begins at home.

Dr. Morris Upton, The Chairman

In all committees the choice of chairman is important and indeed crucial. As we have noticed Dr. Lipton made an unfavorable impression on the orthomolecular psychiatrists and others whom he addressed in California. He told the California audience that he had never used megavitamin therapy and did not treat schizophrenics. Nevertheless, on the strength of having received his Ph D. at the same university where Elvehjem and Woolley discovered that nicotinic acid was the antipellagra vitamin, he launched into a poorly informed attack on the megavitamin treatment and its theoretical underpinning. Since he seemed to be so antagonistic, dogmatically self-assured and, in addition, ignorant about the matter in which he was going to inquire, one of us (AH) requested the APA to remove him from the Task Force on vitamin therapy in psychiatry. This request was rejected on the grounds that the APA Council on Research and Development would insure the objectivity of its subcommittee and monitor its reports.

Recently Leff (1975) confirmed our conclusion that Dr. Lipton was the main author of the report when he stated, "I'd warn people of megadoses for megaperiods" says Dr. Lipton, who wrote the APA Task Force Report." Lipton has, since 1970, been the chief crusader against orthomolecular psychiatry.

Since this was the APA's official position, it must bear full responsibility for the errors and misrepresentations of its Task Force. There can be no question that the Association's highest officers knew that there were cogent objections to the subcommittee chairman whom they had appointed. They made no attempt to remedy this in the meantime. Dr. Lipton was circulating a preview of it, a copy of which came into our possession.

It is a poor augury when the chairman of an important Task Force appears to be prejudiced, but it is worse still if several other committee members should also be suspect.

Dr. Thomas Ban

It is our contention that for a number of reasons Dr. Ban was prejudiced against the megavitamins from the start and that both the content and tone of his publication and his public statements reflect this prejudice. In 1966 Dr. Ban was offered a comparatively small grant of money by the Canadian Mental Health Association to settle the matter of "Hoffer's megavitamin claims once and for all." There is no reason to suppose that the Canadian Mental Health Association directorship was particularly keen for any positive affirmation of this work. It happened that one of us (AH) was a member of the CMHA Advisory Committee and was present when Dr. Ban produced his final research protocol.

At this meeting he outlined a simple experiment comparing nicotinic acid and tranquilizers against tranquilizers only. It was pointed out to him that he had not included provisions for ECT in Phase II patients. He gave assurances that this would be done later on as his studies developed. Another committee member made the same point, but was reminded of Dr Ban's pledge. Dr. Ban also stated that no reports would be released until the entire study was completed. Neither of these pledges was kept.

Since Dr. Ban is a member of the committee responsible for the Task Force's report stating "the credibility of the megavitamin proponents is low," his own credibility is open to similar questioning. He is well known for his
tranquilizer studies and has published many of them Some years ago he informed one of us (AH) that much of his income derived from grants from companies and other sources interested in selling tranquilizers He was thus inherently likely to be caught in a conflict of interest He may well, in all sincerity, feel himself to be wholly unbiased, but one has only to ask what would have happened to many of his grants had he found niacin to be more effective than tranquilizers He would have faced a painful dilemma It was unfair to expect him to view the persistence of megavitamin claims with anything but concern and suspicion Dr Ban's eagerness to disseminate his findings long before his final report appeared was shown by his lecturing professional groups and attacking orthomolecular psychiatry He cannot be considered a disinterested party to the dispute and quite apart from the effect this may have had on his researches, the propriety of his being a member of the Task Force is questionable In any official inquiry he would have been obliged to declare his position Psychiatrists who are supposedly experts on subconscious motivation apparently do not interest themselves in the conscious motivation of those they would have evaluate a new treatment According to Lionel Penrose, who has studied these matters, two members of a committee of five are quite sufficient to bias it in their direction should they choose to collude With Doctors Lipton and Ban on the committee, the odds against a fair and detached report were small; however, there was a third member, Dr. Loren E Mosher.

Dr. Loren E. Mosher

Dr. Mosher was the head of the Center for Studies of Schizophrenia of NIMH This choice was a curious one since he has frequently stated that it is his personal belief that schizophrenia is not a clinical entity and it is not a disease or a series of diseases: He is a disciple of the Scotsman, Dr. R.D. Laing, and prefers to view schizophrenia as a way of life (Siegler and Osmond, 1974) At a meeting in Washington arranged by NIMH (1973) in response to pressure from the American Schizophrenia Association, Dr. Mosher stated forcibly that if every psychiatrist in the U.S.A believed that megavitamin therapy helped schizophrenic patients, he would not believe it. He was being consistent For if he considers that schizophrenia is not an illness, it follows then that no chemotherapy, particularly nutrient therapy, can possibly work While Dr. Mosher's forthrightness may be admirable, he can hardly be considered unbiased for he has made his biases perfectly clear One might, of course, wonder how the NIMH bureaucracy could possibly justify his appointment to the schizophrenia section. It would be just as appropriate for a well-known Christian Scientist to head up a cancer program

Since the APA Task Force was published Dr. Mosher presented a report on Soteria House, a special home for schizophrenic patients for the provision of Laingian-type milieu therapy In this report he shows an interesting difference in attitude toward research data arising from his own research and toward all the data originating from orthomolecular psychiatry Toward his own data he displays a friendly cheerful optimism concluding that Soteria milieu shows great promise, even though at the end of the study period there is not even one index of improvement in which his group was better than the control group The Soteria group required 167 days in residence compared to 21 days' residence in a psychiatric ward by the control group, a difference of 800 percent. This Mosher truthfully describes as being significantly larger There was no difference in global psychopathology after one year between the two groups But in spite of the fact that in every index of change there was no difference Mosher concludes there is a trend favoring their approach The difference, so slight it does not appear in any of the tests, is maximized in his sanguine report. In striking contrast Mosher as a member of the Task Force adopts an
entirely different stance. Here he finds no amount of data, no matter how great the difference, is persuasive. Here he minimizes the difference. Had Mosher remained a pure critic as he was as a Task Force member his position would have remained less assailable, but having exposed himself to public scrutiny by publishing a report he has shown his undoubted bias against orthomolecular therapy and toward milieu therapy. This is consistent with his remark several years ago that he would not accept megavitamin therapy as valid even if every psychiatrist in the USA did.

In April 1971 AH wrote to Chairman M. A Lipton requesting that he disqualify himself as chairman because of his undoubted bias. He did not reply. June 8 1971 AH wrote to President R S. Garber, American Psychiatric Association, repeating this request. These letters are reproduced in the appendix. Since then the public activity of at least three committee members, Ban, Lipton, and Mosher, have confirmed our suspicions that no prudent person or organization would have chosen them as unbiased investigators in an important public issue.

Dr R Wittenborn, Ph D., was a consultant of the committee and probably one of its least biased sources. It is not certain, however, that NIMH was of this opinion when he was given five hundred thousand dollars to conduct his study. Several years earlier, we were told by a well-known U.S. psychiatrist from the Midwest that he had been approached by the NIMH to direct this study. He agreed on condition that one of us (AH) was retained as a working consultant for the duration of the study. He was promptly dropped from further consideration. Apparently Dr Wittenborn did not make this demand; as a psychologist he may have been less aware of the high feelings generated among psychiatrists by megavitamin treatment. However, he was not a member of the committee and so cannot be held responsible for its conclusions. Of the five committee members, then, three by their own words and deeds seem to us to have been grossly biased against the treatment they were supposedly investigating with complete impartiality. In Lionel Penrose’s view, which we have already noted, this would make it almost certain for the final outcome to reflect the views of the majority.

The committee represented two institutions: (a) the National Institute of Mental Health which since 1967 has been as antagonistic toward the megavitamin approach as it was against tranquilizers in 1955—it had two representatives, Dr J. Levine and Dr L R Mosher; (b) the North Carolina Department of Psychiatry, College of Medicine, with Dr M A. Lipton, Chairman of the Department and of this committee, and Dr F J. Kane, one of his professors. Dr Kane was co-author with Dr Lipton of the privately circulated attack on orthomolecular psychiatry in 1970 before the committee completed its studies or published its report in 1973. It is unlikely Dr Kane could have differed significantly from his chief even had he wanted to do so.

The appearance of bias is so powerful that even if there had been none the committee was incapable of submitting a objective and fair report.

Recently Emanuel (1975) wrote; “Teachers and students alike delude themselves as to the worth of what is transmitted but because the teachers often play a role in the subsequent career of students and become prestigious centers attracting the most able, these delusions become self-fulfilling prophecies. In no branch of medicine is there less to transmit than in my specialty—psychiatry—by supervision, correctness of approach and doctrinal conformity to an extent sometimes more appropriate to a theological seminary. Probably the best training for any psychiatrist and perhaps internist too would be a year or more in general practice where exposure to a wide range of human suffering and human responses to it would teach a sense of proportion.”

Emanuel’s strictures against professors may just as aptly be applied against this committee. It is not our opinion alone that committees can inhibit progress in medicine. Lasagna (1967) recently wrote,
"Indeed, it is not impossible that a series of inaccurate opinions from a number of distinguished experts would snowball into an overwhelming endorsement or condemnation of a drug. Jain (1975) in a serious discussion of ethics refers to the enormous power wielded by establishment committees. He discusses the relationship of physicians to physicians, but his views are just as applicable when one considers the relation of new to old ideas. He lists four reasons why committees representing old ideas resist new ideas: (1) human nature (i.e., interpersonal hostility); (2) territorial imperative (i.e., the threat of the new ideas against old, widely established ideas); (3) financial factors; (4) the generation gap.

The resistance of well-established ideas no matter how mistaken against new ones is probably the major reason for the committee bias. Their tranquilizer-only idea of treatment is coupled firmly to establishment professors, directors of research and administrators. There may be a feeling that giving up the old ideas will mean losing their place in the hierarchy of the establishment. So far not a single professor of psychiatry has given public support to orthomolecular psychiatry even though a substantial number have given it private support.

Jain then lists the difficulties facing new physicians. The same fate meets new ideas. We will repeat the difficulties he lists, except that we are referring to ideas. "Doctors controlling the ethics committees are usually from the establishment and it is no use complaining to them." "Most of the maneuvers by the doctors in the establishment are done under the name of the university or hospital or a committee to which the doctor belongs. The result is that on the surface, decisions appear to be based on sound medical reasoning not on personal bias which can only be uncovered after exhaustive investigations." He then quotes Sir Clifford Allbutt, "Unfortunately, the same kind of medicine is played with the cards under the table in the intimacies of medical counsels. Who is there to note the significant glance, the shrug, the hardly expressed innuendo of one or other of our brethren? Thus, we work not in the light of public opinion, but in the secrecy of the chamber."

Did the Procedures Used Provide for a Fair and Objective Examination of the Data?

The bureaucratically inclined sometimes hope that by proper procedures the effects of personal peculiarities and shortcomings can be avoided. These hopes are frequently disappointed. In this case, however, inadequate procedures combined with a committee three out of five of whose members were clearly prejudiced against megavitamins made an unbiased report most unlikely. Because there was no orthomolecular psychiatrist on the committee and none was asked to attend its deliberations, nobody checked to see whether the literature had been examined properly, summarized fairly, and presented intelligently. The committee's actions suggest that they relied upon the inertia of their colleagues to avoid criticism of their report. They appear to have assumed that their task was to prevent the public and the profession from worrying itself unduly about orthomolecular psychiatry. In other words, the end was to encourage the reader to adopt Dr. Mosher's avowed position, which as we have already noted was that even if every psychiatrist in the United States believed in megavitamins, he would still not do so. The means by which they set out to achieve this will be examined in detail. Unluckily, there are many errors in the Task Force Report and we keep finding new ones, yet unless these errors are exposed the casual reader unacquainted with the literature can easily be misled into supposing that a Report published with the approval of the American Psychiatric Association must be accurate and truthful.

It may seem unlikely that a responsible professional organization such as the APA would give one of its subcommittees such license and pay so little attention to the composition of that committee, but at the time when these
matters came under the APA's scrutiny, Washington was heavily infected by the Watergate atmosphere. Minority views were not respected; "dirty tricks" were an accepted necessity of political life; authority, whether presidential or professional, was looked upon as limitless. It was assumed that the big battalions had not only the right but also the duty to trample upon those who disagreed with them, using any means available. Orthomolecular psychiatry was a nuisance to both the APA and the NIMH, and some members of both these establishments apparently believed that anything that would damage it would be doing a public service. It should not strain credulity that if the CIA or FBI can sometimes be overzealous in the defence of what many conceive to be the public good, less prestigious agencies should do likewise.

The Title
The Task Force was appointed to study vitamin therapy in psychiatry as the title of the report suggests. Instead, it attempted to deal with the megadoses of vitamin B3 only, and entitled the report erroneously "Megavitamin and Orthomolecular Therapy in Psychiatry." Orthomolecular therapy was not examined because the committee stated that they knew of no way by which it could be tested.

The Report
We have read the report carefully and then compared it with the original sources. When this was done, our early impression that it was biased and hostile in tone was confirmed. There are many errors and omissions, while its scholarship is of such low level that it cannot be trusted. In the following pages we will show this by using a point by point examination of the examples of bias and error and sometimes sheer muddlement.

Introduction
(1) On Page 5, the report claims that we "shifted" our position (The reader should have a copy of the Task Force Report #7 before him, read the whole booklet, then reread each page as we continue with our discussion.) In science the word "shift" is usually used as a pejorative term implying that theory or practice is constantly changing so that duplication of experiments and refutation of theories is impossible. This is not so. In our original report (Hoffer et al., 1957) we listed a number of possible mechanisms by which vitamin B3 could work. These were: (1) Elimination of the vitamin deficiency. We did not think then nor do we think now that schizophrenia is due to a vitamin deficiency. The concept of a vitamin dependency had not been developed, but when it came along it created the possibility that some schizophrenics might be vitamin B3 dependent. (2) Cerebrovascular effects. (3) Mass action on cellular metabolism. (4) Placebo effect. (5) Depletion of methyl groups. (6) Restoration of acetylcholine esterase activity. (7) Inhibition of DPNase (now called NADase) activity. (8) Acceleration of destruction of a schizophrenic toxin. (9) Direct antagonism to a schizophrenic toxin. We, therefore, have put forward a number of theoretical possibilities for further inquiry.

As we gained more experience with our treatment, we improved it. It would surely be unreasonable and unenterprising to continue recommending an original pioneering effort and to use exactly the same dosage and exactly the same substances decade after decade. If the same rule were applied to tranquilizers, psychiatrists would still be using the doses of chlorpromazine and reserpine recommended in 1955. Treatments, if they are any good, grow and evolve. For some reason the committee seemed to expect us to stand with the original doses of the original vitamins as they were used in 1952, thus ignoring the entire historical development of the orthomolecular treatment. It must be a matter of opinion as to whether the committee's expectations were naive, perverse, or both.

(2) Hormones are generally not used by orthomolecular therapists unless there is a definite indication such as hypothyroidism, diabetes, etc.

(3) Vitamin B3 was never considered a
competitor against tranquilizers. This is one of the notions developed by the committee. Our original double-blind experiments began before tranquilizers became available. They were, therefore, not included in the design of these experiments and were not used for these studies. They were used in conjunction with the program for other patients and are still so employed using the standard indications. We have been continually surprised by the number of psychiatrists who advise their patients that we never use tranquilizers. When pressure from their patients is great, they have frequently placed them on inadequate low closes of vitamins and promptly discontinued the tranquilizers. This has, on occasion, caused relapse for which the vitamins were blamed. We have always made it clear that even with correct closes the response can be slow.

(4) On Page 6 they correctly refer to the orthomolecular view that the schizophrenias are a group of illnesses with different biochemical aberrations, but, thereafter, they ignore this basic view and do not distinguish between acute and chronic patients. In 1957, Hoffer et al. concluded, “although many chronic ambulatory schizophrenic persons have responded to nicotinic acid therapy, similar results have not been obtained with chronic schizophrenic persons in mental hospitals.” This suggests that either the chronic process is different from the acute process, or that it is more malignant.

“Lack of response of nicotinic acid indicates that doses have been inadequate or that the biochemistry and physiology of schizophrenic persons differ in some hitherto unsuspected manner. The differences may be due to irreparable enzymatic damage as a result of a long inhibitory process, irreparable functional destruction of vital cerebral centers, the presence of biochemical mechanisms not reversible by nicotinic acid, or an inability of the patient in chronic stages of the disease to assimilate nicotinic acid adequately or to utilize nicotinic acid in the same way as the patient in the acute stages. Perhaps the answers to these problems will come with future research.”

Cinader (1975), an immunologist, is well aware of the importance of individual variation in disease and therapy. In discussing controlled, comparison clinical trials he writes, “A treatment selected by clinical trial may be inappropriate for some patients who cannot be identified in advance. Such treatment failure is due to the heterogeneity of the disease or of the response of individuals to the disease or the treatment or is due to both factors. A better definition, that is, identification of homogeneous disease entities, is an age-old objective of clinical research.”

We were aware of these factors many years ago and always described as carefully as possible (within space limitations of medical journals) the kind of patients we had treated. The committee ignores this surely not out of ignorance.

(5) Page 6—The committee continually quibbles about terms. There is certainly nothing orthomolecular about I:CT or about foreign molecules such as tranquilizers, but there is no reason why a name designed to direct attention to correction of metabolic disorders by nutrient therapy should be dropped because these other non-orthomolecular methods are helpful adjuncts.

(6) Page 7—The committee accuses us of making categorical statements without systematic documentation. This is not so. Orthomolecular therapists have provided large quantities of data based upon double-blind, clinically controlled, follow-up, and other studies. The only limitation has been the modern style of medical journals to reject papers they deem too long. Hawkins’ statement was a summary of a vast experience. Not one of the committee had ever personally treated schizophrenics using the full treatment. They are in no position to be critical. Even if Dr. David Hawkins had given them 2,000 case histories, would they have been any more receptive?

By quoting our statement on prevention out of context, they deny readers an opportunity to see how this hypothesis was derived. Before flour in the
U.S.A. was enriched with small quantities of nicotinamide, it was thought that pellagra could not be influenced in so simple a manner. But enrichment of flour nearly eradicated pellagra, a vitamin B₃ deficiency. The use of larger doses might prevent development of vitamin B₃ dependency. Since we have already seen this in children of some schizophrenic parents, our suggestion is hardly fanciful. The committee may not agree, but since they have never used vitamin B₃ in this way their criticism is founded on their personal opinion and nothing else.

(7) Page 7—While attacking our suggestions for prevention they make such unnecessary errors as referring to the Huxley Institute for Biosocial Research as the Huxley Society and to the Academy of Orthomolecular Psychiatry as the Association of Orthomolecular Psychiatrists. There are many other similar examples of simple carelessness throughout this document which should make readers wary. Authors who cannot get names, titles, and dates correct may be even less reliable in more complex matters.

(8) Page 8—We have received a favorable press perhaps because we have been open and honest with reporters, but our discussion with writers did not occur until they sought us out and many years after publications in medical journals. We have never had the same access to the media as the APA with its great resources and paid staff members doing public relations. So far the Task Force Report has not been very warmly received. This may be because many science writers have done their own inquiries and have concluded, as we have, that this report is not worthy of an important subject which bears on the lives and well-being of thousands of suffering people.

(9) Page 8—Lines 16-19 Where the committee writes, "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," this is false. So far, no one has repeated the original double-blind experiments. These used acute and subacute cases with a combination of vitamin B₃ and ECT in comparison to placebo and ECT. None of the reports listed in the Task Force Report followed these procedures.

However, their statements on Page 8, "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 proven 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," are not correct either. If this was their opinion one wonders why they continued to write a report. It is possible to replicate far more complicated treatments than those which we have described, and very few medical or surgical treatments are completely stereotyped and without individual variation. The studies must be published and those who wish to replicate them must first examine what was in the original work. Where there is doubt, or if necessary details are lacking, the ethical investigator, aiming at replication, approaches the original authors and seeks their advice and clarification. This was not done, whether due to carelessness, incompetence, or lack of good will is a matter for the reader to decide.

(10) Page 8—We have never claimed that vitamin B₃ is the crucial variable. It is one of several crucial variables. As many of our studies show, ECT and other chemotherapy can be crucial. We cannot be sure why the committee chose to imply that we claimed that B₃ was the crucial variable; perhaps they felt that unwary readers, being persuaded of this, would fail to notice that important treatment components had been omitted. Whatever the committee's motives its members overlooked the fact...
that if they condemned a useful treatment unfairly the losers would not be their professional opponents (us and our colleagues), but tens, perhaps hundreds of thousands of patients. What in other circumstances might be considered clever debating tricks becomes less clever and more irresponsible here.

(11) Page 8—Whenever the committee refers to the negative double-blind experiments its Report employs such flattering terms as "the rigorous double-blind studies with vitamin B3" and "the careful attempts at replication deal with the explicit procedures." If an experiment which uses chronic patients rather than acute or subacute ones, which ignores ECT as we originally used it, and which uses entirely different evaluative procedures can be called a careful attempt at replication, then there is little hope in psychiatric research. The committee adopts the rule that every experiment purporting to be double blind which yields negative results is by definition "careful, rigorous." They do not, however, apply the same rule to the original experiments done under our direction in Saskatchewan because presumably they consider that we were so biased that even the sacred double blind was not to be trusted.

We doubt whether this committee was so ill-informed as not to know that for all the faith placed in them, double-blind studies can be badly designed and executed so that false conclusions result. For example, the University Group Diabetes Program (UGDP) concluded that biguanides (Phenformin) increased cardiovascular mortality in diabetics. This was an expensive controlled experiment, but recently Biron (1975) wrote, "There were so many flaws and biases in the design and execution of this trial, that experts in experimental design who meticulously appraised the methodology and the results believe that there are few reasons to ascribe the higher death rate to the oral drugs, but many reasons to attribute them to differences in the numerous pertinent risk factors that were not measured at time of entry into the study." In a satirical letter Biron (1975a) referred to a Sugargate coverup, pointing out that the data could equally well be interpreted as showing that insulin and glycemia control are more dangerous than placebo. But the UGDP scientists nowhere discuss this finding. In other words, double blinds do not guarantee that the results of an experiment will be objective or accurate.

Restak (1975) attacks most double blinds from another approach supporting Hoffer and Osmond's (1961, 1963) earlier views Restak wrote, "one thing fundamentally wrong is the design of the typical experiment using human subjects. All too often such experiments are set up in a manner that almost guarantees emotional distance and alienation between the experimenter and his subjects. It is not unusual for many contemporary researchers to have no personal knowledge of the identity of the participants in their own experiments which are carried out via intermediaries. All too often scientific objectivity is distorted to include callousness and lack of concern for the human aspects of research."

Several of the psychiatrists who were clinically involved with the patients in Wittenborn's and Ban's experiments later became orthomolecular psychiatrists. They saw improvement not visible to the directors of the study because the directors saw only paper and numbers, not patients. Their clinical observations were more meaningful than the APA conjectures.

(12) Page 1—It would seem to us that one doctor experienced with a new treatment would be much more trustworthy than 1,000 who had never used it. If the committee wishes to play the numbers game, they might explain why over 1,000 psychiatrists had the temerity to diagnose Senator Goldwater without ever having examined him.

On Pages 1 and 2 the committee extracted phrases or sentences from the original reports in such a way as to bring out the worst possible interpretation of what was said. The only way to prove hostile bias is to examine the papers which have been published, to abstract
them briefly, and to highlight the conclusions therein. We have, therefore, referred to a large number of original reports as well as to the corroborative papers which have been published. These are discussed in an appendix so as not to burden the reader unduly. But these reports should, be examined in detail and compared with the committee's interpretations and conclusions. As will be seen, the committee review has been marred by errors of omission, of distortion, by incorrect references to the literature, by bias obtained by a careful selection of the literature and of the data presented in any one paper. Thus, from about 26 original reports they were seemingly unaware of eight, but they had access in the literature to 19. Out of about 29 corroborative reports they should have known about 15, but referred to three or less. But they did discuss any study which was negative no matter how badly it had been done. In one case they were instrumental in having one such study published even though there had been no attempt by the authors to publish until now. It appeared in a free journal edited by one of the committee and distributed by NIMH, Washington.

Because the committee ignored so many reports favorable to orthomolecular therapy while paying attention to any negative report, however obscure, it becomes possible to give their bias a mathematical form by using a frequency distribution and the null hypothesis. This shows:

<table>
<thead>
<tr>
<th>Reports Favorable</th>
<th>Reports Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred to by committee</td>
<td>23</td>
</tr>
<tr>
<td>Not referred to</td>
<td>23</td>
</tr>
</tbody>
</table>

Chi so 10.00 n c 0.001

NAD reports are not included since NAD is neither nicotinic acid nor nicotinamide. Not every favorable report was counted. This shows that the betting odds that the committee surveyed the literature fairly is less than .001, or one in a thousand that such a bias occurred by chance alone.

(13) Page 3, 4th paragraph—The committee seems to be, or wants to appear, naive when discussing the role of pharmaceutical companies in the popularizing of drugs. At the present time drugs hardly ever become popular unless there are forces which keep bringing them to the attention of the medical and lay public. When a pharmaceutical company has a use patent on a drug it is able to invest heavily in its advertising knowing that other companies are prevented from profiting from the original company's efforts. Advertising consists of spreads in medical journals, frequent visits from friendly, personable, well-trained salesmen who leave samples and literature, and articles sponsored in medical journals. Drugs which are not patented are known in the pharmaceutical jargon as "orphan drugs." They are owned by no one and therefore are not promoted by any particular companies. The vitamins are orphan drugs. This means that there are no detail men, no massive skillful advertisements to keep the vitamins before physicians as therapeutic agents. An example is the promotion of atromid, a British drug used for towering cholesterol and triglycerides. Nicotinic acid, the orphan, is an even better broad-spectrum hypolipidemic substance. Nearly every physician knows about atromid which is constantly before physicians in their medical journals in three- to four-page spreads. There is no advertising whatever for nicotinic acid, and very few physicians are aware of its lipid-lowering properties.

The committee admits there is a grain of truth in our charge that orphan drugs are less impressive to psychiatrists than those that have been massively advertised. They doubt whether there is much to this: "If however they contained the full truth, psychiatry would indeed be in a sorry state, gullible to the seduction of advertisement, pitiful in its naivete" and so on.

We have not counted any of the papers in Orthomolecular Psychiatry edited by D R Hawkins and L. Fouling (1973) since higher chi squares would be meaningless.
It is for our readers to judge whether the committee may not have been over-optimistic about psychiatrists' capacity to resist advertising if they are correct then many drug companies are wasting a great deal of money buying up space in the journal of American Psychiatric Association and the APA's many other publications. It is possible that these vast companies are so slipshod as not to know the benefits they gain from advertising.

Other psychiatrists are not quite as naive as this committee for example, Samuel Gershon and Baron Shopsin (1973) in their book on lithium write, "another important factor contributing to the delay in using lithium for psychiatric purposes is undoubtedly that its ready availability rendered it commercially non-profitable; drug companies neither investigated nor promoted its use Rowell Laboratories, a small pharmaceutical house in Baudette, Minn, had the foresight and the initiative to support the necessary investigational work finally leading to the commercial marketing of lithium in 1969." So far no Baudette-company has come forth for vitamins and they still remain orphans. However, a large number of pharmaceutical companies, not listed among the giants, do provide the vitamin tablets necessary for orthomolecular therapy.

The same conclusion was reached by a report released by the National Institute of Mental Health in 1970 (revised in 1974) entitled "Lithium in the Treatment of Mood Disorders." This report is introduced by Bertram S Brown, Director. He obviously does not disagree with this as there is no disclaimer.

On Page 1: "In the United States, however, neither the first report in 1949 nor the impressive Danish work published in 1954 aroused any research interest in lithium." "This situation seems strange at first glance, for the discovery of the psychoactive properties of lithium was of great significance."

On Page 2: "Lithium itself, moreover, was of no interest to the drug companies until quite recently, because it is a natural product and therefore unpatentable. Thus, the resulting lack of commercial sponsorship further clouded recognition of lithium's potential."

Parsons (1974), a pioneer in the development of nicotinic acid as a broad-spectrum hypolipidemic agent, in reply to a hypothetical question, "why is niacin with its long and impressive record not used more widely by clinicians?" stated, "as a non-patentable drug it has not enjoyed the commercial promotion of other lipid-lowering drugs." Parsons himself is employed by a pharmaceutical house and is speaking from personal knowledge on these matters.

The committee winds up Section II by suggesting that megavitamin therapy has little scientific support and that legitimate empirical attempts at scientific replication have failed. There are two main classes of scientists: (a) those like of Linus Pauling, Nolan D C Lewis, H Klüver, Gyorgyi, and others who make original contributions; (b) those who follow along and re-plough fields already opened. Of the committee members none are in the first rank. They may be excellent representatives of the psychiatric establishment, but are not noted for their scientific contributions. This may be why this entire APA report reads more like a polemic as one would find in Time Magazine, rather than like a learned discussion as might appear in Science.

The committee finally writes, "legitimate empirical attempts at scientific replication have failed." The term legitimate is an unusual word in a scientific document. Presumably, the committee considered all the positive studies illegitimate.

The statement that the empirical attempts to replicate failed is untrue for as we shall show none of the studies extolled and praised by the committee have made the slightest attempt to replicate.

(14) Page 5—The committee wrote, "an alternative hypothesis proposed by" Hoffer. "They ignored Osmond and; (Smythies in this reference perhaps: because they were then not aware that; Smythies had found evidence supporting"
the use of vitamin B3. Perhaps the intent was to dissociate Hoffer from Osmond and Smythies. They then state that the oxidation of adrenalin to adrenochrome was demonstrated long before we referred to it, but neglect to point out that we discovered the psychotomimetic properties of adrenochrome. Oddly enough, the original work was completed at the University of Saskatchewan under the first professor of biochemistry, Dr. Roger Manning, University of Saskatchewan at Saskatoon, in 1935.

(15) Page 6—The committee refers to only one out of nine possible explanations we gave for the action of vitamin B3, i.e., the methylation ideas. This, as we have already shown, is one of many possibilities. They then state "not only is there no evidence for adrenochrome formation in vivo, but the psychotomimetic properties of adrenochrome have also not been replicated." Both these statements are demonstrably false; there is a substantial body of evidence that adrenochrome is made in vivo and this has been summarized in detail in our book The Hallucinogens (Hoffer and Osmond, 1967). This evidence may not satisfy the committee, but since they did not refer to our book, we must assume that they were ignorant of it and so are in no position to judge.

The last part of their statement is simply untrue. Double-blind experiments in Prague confirmed the hallucinogenic properties of adrenochrome. It is listed in NIMH-sponsored literature as an hallucinogen and is so recognized by Ban (56, APA Task Force Report Reference) who wrote "after a considerable dispute, however, the psychotomimetic properties of adrenochrome were confirmed." Yet here is Doctor Ban, a co-signer to a report which states that its psychotomimetic properties have not been confirmed. Several years ago he and one of us (AH) debated before a group of psychiatrists in Newfoundland. When AH quizzed him about this statement he admitted that adrenochrome's psychotomimetic properties had been confirmed. What is the point of the APA publishing reports which even those who sign them agree are untrue? Surely Lincoln's warning has not been wholly forgotten in Washington where the difficulties involved in fooling all of the people all the time have been shown up vividly in the last few years.

(16) Page 6, second paragraph—"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 g per 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. Re-admission 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."

We were hoping to find one of our papers abstracted correctly. But this was not to be. In this paragraph the committee confused two quite different reports, the original double-blind report of 30 cases, and a second follow-up study on a larger group most of whom had not been treated in the double-blind experiment.

(17) Page 6—The committee writes, "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." They did not include the important fact that 21 of the
placebo patients also received ECT and 15 of the vitamin group received ECT. It seems to us an attempt to neglect ECT as an important variable. Then they continue, "In this study, the nicotinic acid group had significant improvement in the hospital."

What they did not say was that 31 out of the 39 improved compared to only 18 out of the 43 placebo group. We reported this was a highly significant difference. They also did not record that doctors not in the research group were allowed the option of requesting the medication given to their patients be decoded if they felt there was insufficient progress. This was requested 18 times from the placebo group and once from the vitamin group (chi squared = 19, p < 0.001). Then the committee continues, "but little difference in the relapse rate."

This is an astonishing distortion of what we reported, equivalent to calling black, white. We pointed out that over the 5½ years of follow-up (June 1953 to December 1958) all patients from the second double-blind controlled experiment were given either 1 g of nicotinic acid or 1 g of placebo per day after discharge. The two follow-up groups were randomized. We, therefore, had four groups: (a) placebo in hospital and after discharge; (b) placebo in hospital and 1 g of niacin after discharge; (c) niacin in hospital followed by placebo; and finally, (d) niacin in hospital and after discharge. We showed results as follows:

<table>
<thead>
<tr>
<th>Group Treatment</th>
<th>In Hospital</th>
<th>After Discharge</th>
<th>N</th>
<th>Percent of group requiring readmissions after discharge, year after discharge</th>
<th>No. of 5-year cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>placebo</td>
<td>20</td>
<td>1</td>
<td>2</td>
<td>40 21 55 50</td>
</tr>
<tr>
<td>placebo</td>
<td>niacin</td>
<td>8</td>
<td>2</td>
<td>13</td>
<td>25 25 30 0</td>
</tr>
<tr>
<td>niacin</td>
<td>placebo</td>
<td>29</td>
<td>3</td>
<td>36</td>
<td>24 17 13 41</td>
</tr>
<tr>
<td>niacin</td>
<td>niacin</td>
<td>25</td>
<td>4</td>
<td>8</td>
<td>12 6 10</td>
</tr>
</tbody>
</table>

It is obvious that the best record was achieved by the niacin-niacin group and the worst by the placebo-placebo group. The other two groups were in between.

We also reported that out of 118 patient-years in community on niacin there were seven readmissions, while from 182 patient-years on placebo there were 60 readmissions (chi square = 20, p < 0.001).

The 20 placebo-placebo group required 16 readmissions totaling 9.1 years while the 62 patients on niacin at one time or another required 39 readmissions for a total of 11.2 years. Had they required the same number of days in hospital relative to the size of the group they would have required 28.2 years.

Finally, we concluded, based upon six indices of improvement: (1) condition in community, (2) number readmitted, (3) number of readmissions, (4) number well, (5) number much improved, (6) five-year cures, that the order of decreasing merit of treatment was as follows: niacin-niacin > placebo-niacin > niacin-placebo > placebo-placebo. There was, in fact, a very significant difference with those patients on niacin in and out of hospital doing much better. Three five-year cures out of 20 on placebo = placebo (15 percent) is surely different from 19 out of 62 or 30 percent in the niacin groups. What did the committee read?

Then they added, "The only patients who had a significant improvement with nicotinic acid continued after discharge; from the hospital were seven acutely ill females."

It seems more charitable to ascribe this statement to a deliberate attempt to confuse rather than to accuse the authors of being unable to read. This is what AH wrote on page 54 of his book (1962): "A total of 33 patients received nicotinic acid after discharge. Of the nineteen rated improved, only nine retained this!"
status, but out of fourteen rated unimproved on discharge, seven improved. This latter group, although small, is the only group which differs significantly from all the other groups listed in Table 24. This table showed the following:

<table>
<thead>
<tr>
<th>Treatment in community</th>
<th>Discharge evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community N</td>
<td>%</td>
</tr>
<tr>
<td>19</td>
<td>(a) improved</td>
</tr>
<tr>
<td>14</td>
<td>(b) not improved</td>
</tr>
<tr>
<td>Other treatment 31</td>
<td>(a) improved</td>
</tr>
<tr>
<td>18</td>
<td>(b) not improved</td>
</tr>
</tbody>
</table>

What this table showed then was that out of 14 patients discharged as unimproved on 1 g of niacin per day, seven became well or much improved after at least one year treatment in the community. In contrast, out of 18 discharged as not improved not given niacin but given other treatment, only one became well or much improved. On the other hand, out of 19 discharged as improved and continued on 1 g of niacin, only nine remained well or much improved while out of 31 evaluated improved or discharged but not given niacin only 13 remained well or much improved.***

This shows that 1 g per day is enough to produce improvement in some and not in others, which is not surprising. It has always been clear there is an optimum treatment and follow-up dose. We find the committee's capacity to distort our findings incomprehensible and are at a loss to account for it. It appears to be a deliberate attempt to mislead unwary readers in the hope that they would not compare the report with the original source if this was the intention then it was doubly deplorable for apart from the falsification it underestimates the curiosity and zeal of some members of the public. It suggests an arrogant and supercilious approach to both the profession and the public.

(18) Page 7—The committee stated, "Positive claims for the efficacy of nicotinic acid have been made by other workers." They then list a number of published studies, while ignoring a number, and list four reports they had never read. These were APA references #33, 36, 37, and 40. These were papers read at the Brunswick Hospital meeting, but never published. None of the committee members were present. This is an example of padding. It is customary not to refer to unread papers unless this is noted in the text.

(19) Page 8—The committee made the following criticisms of megavitamin work:

1. Contamination of studies by frequent use of ECT. We have always shown dearly that ECT was an essential component of treatment for Phase II patients. It is odd to term an essential ingredient a contaminant. The committee still attempts to play down ECT, presumably to further their contention that vitamin B3 is the crucial variable.

2. A nonrandom or biased selection of the small numbers in our studies compared with the total population at risk. For the first two double-blind studies every patient admitted who was schizophrenic was taken into the study, provided that his therapist allowed this to happen. This is the way most studies are done. We do not know of any studies where a random selection of all admissions has been used. All that is required by classical double-blind methodology is that the allocation of patients into the treatment groups is randomized. The committee has created some new rules to suit their fancy: The size of the groups treated was adequate to test the null hypothesis and was
somewhat larger than sample sizes used by Ban and Lehmann. If our work is questioned on this count the same criticism should be levelled at Ban and Lehmann (Ban 1972) is uncertain whether 15 to 30 patients in any group can yield any conclusion at any acceptable level of thoroughness.

3) The lack of clearly specified initial diagnostic groups or systematic rating of patients. This is false. The reader must read our original papers where we described in detail diagnostic criteria and evaluative methods used.

4) The failure to specify chronicity. This is false as any examination of our published data shows.

5) Nicotinic acid was never the only treatment given. We have repeatedly emphasized that vitamin B3 was one of the main treatments in any series. However, we have seen hundreds of patients recover on vitamin B3 alone. We are prepared to demonstrate these to any physician who wishes to see our patients and their clinical records. So far over 50 physicians have done so and are now practicing orthomolecular therapy.

6) "The number of patients in the follow-up sample were small." This is a misleading criticism. How many 10-year follow-up studies have been reported with tranquilizers? We have recently seen one. Perhaps the committee will bring others to our attention. "Treatment and comparison groups were not matched as to pre-treatment prognosis." This is another after-the-fact suggestion which makes it look as if the committee was searching desperately for every possible criticism of our work. They were much less critical of the Wittenborn and the Ban and Lehmann double blinds which were not double blind. Had they found such errors in our work there would have been no end to their comments. To be fair, in the original protocol Ban termed his study "semi-blind," but he conveniently ignores this in this report.

7) The committee is critical because in our original double-blind studies we did not compare vitamin B3 against tranquilizers. We would have done so, but tranquilizers did not come into general use until 1957. By then our first experiment was completed and our second one nearly completed. Since then we have published many reports comparing vitamin B3 as a treatment component against tranquilizers alone.

8) The final attack is a repetition of earlier mistakes. The committee wrote, "In the first one the patients received the drugs only in hospital, did not improve significantly in hospital but had a lessened tendency to relapse for four years after discharge." The committee manages to be confused about even elementary reports. We concluded that the vitamin B3 patients were better off than placebo patients on discharge, but that at the end of one year they had reached a one-year recovery rate twice as high as the placebo group. This the committee terms "a lessened tendency." As usual they play down the positive and emphasize the negative more like hostile attorneys than scientific inquirers. Then they say, "In the second study the reverse is true: there was an improvement in the hospital, but the subsequent relapse rate was the same." As we showed earlier the second half of this statement is false. The committee then remarks, "These differing results are hard to explain." Perhaps so; if one cannot read almost anything must be perplexing. Both studies showed that patients on vitamin B3 therapy improved in hospital and had a significant decrease in relapse rates. But the committee falsely concluded white is black.

We do not find any inconsistencies in the statements in the last paragraph on Page 8. It is true a few patients recover very quickly on vitamin B3 therapy, but that most patients recover more slowly. This is also true of tranquilizers. We do not understand why this is considered an inconsistency. It is a general phenomenon of all therapeutic drugs. But with orthomolecular therapy a large proportion of patients recover fully to become doctors, lawyers, professors, farmers, white collar workers, and so on. We have yet to see one schizophrenic physician become normal on tranquilizer therapy only.
Page 9—The committee finds another inconsistency between a report by Saarma and Vasar (Ref 46) and their reference to O'Reilly (Ref 47). They say Saarma et al cited negative finds for nicotinic acid in acute schizophrenia. This is what Saarma said, but the committee knew the O'Reilly study was on chronic patients only since they listed the title of his paper accurately as "Nicotinic Acid Therapy and the Chronic Schizophrenic." (See Ref 47.) It was also so listed by Saarma and Vasar who probably missed the word in their proofreading.

Page 9—In complaining about our original methodology the committee cited three examples. The first one is from Hoffer et al (1957) where they extracted sentences from a paragraph: "When the adjustment rating is not available for a particular patient but his progress after discharge is adequately known, an impressionistic score is given, but the committee carefully omitted the rest of the statement: "(for example, good adjustment or poor adjustment) These findings, however, are excluded from the mathematical evaluation of progress," Surely this is a most important statement to leave in, but if the committee had done so they would have removed one of their examples of questionable methodology. However, this evaluative method was used for nine patients out of the 30 as follows: (a) from the placebo group four had poor adjustments; (b) from the nicotinic acid group, two; (c) from the nicotinamide group, two—both being then in mental hospital This exclusion of a crucial qualifying sentence suggests that either deliberate falsification or massive subconscious bias was at work.

The APA Research Committee should have been more diligent in monitoring its Task Force.

The second example of the committee is an attack on Chinaglia (1965) and the third example is an attempt to smear us. The committee writes, "Hoffer in a broadside for public distribution published in 1965 says, 'It (nicotinic acid or nicotinamide) does not cause any harm during pregnancy) to babies There is evidence that it can protect babies against the harmful effects of other substances.'"

The New World Dictionary, Second College Edition defines broadside as follows: "(1) The entire side of a ship above the water line; (2) (a) all the guns that can be fired from one side of a ship; (b) the simultaneous firing of these guns; (3) a vigorous or abusive attack in words especially in a newspaper; (4) the broad surface of any large object; (5) (a) (originally) a large sheet of paper printed on one side as with a political message or in 17th century England a popular ballad also broadsheet; (b) a large sheet of paper printed on one or both sides as with advertising and often folded."

We have never mass circulated any communication, but have, as a policy prepared printed information letters which are sent only to lay and professional people who have written to us for information. Nowhere in the precise definition of broadside is there anything remotely resembling anything we have done. However, definition #3 fits closest of all the APA Task Force Report.

In our personal communications, which these letters were, we did not refer to literature references. For the committee to treat these private letters as if they were documents published in a medical journal is grossly unfair.

We have been using niacin on several thousand cases since 1952. A large number of females have become pregnant and had normal children while on niacin. There has been not one infant born to these patients with any congenital defect.

Safety, Side Effects, and Relative Lack of Toxicity of Nicotinic Acid and Nicotinamide, A. Hoffer (19696)

In this paper, AH differentiated between side effects which may be a nuisance and toxic effects which are potentially harmful. Side effects include: (1) Vasodilation of the anterior part of the body with a sensation of heat and itching.
(2) Nausea occasionally followed by vomiting.
(3) Rarely activation of peptic ulcer
(4) Rarely dry skin and very rarely increased pigmentation of flexor surfaces
(5) Headaches

They are not dangerous and are easily controlled by lowering the dose or using other means. Possible toxic reactions of nicotinic acid include liver toxicity which is rare, occurring about one-tenth of the frequency with which it appears with tranquilizers. It may alter the sugar-tolerance curve and may cause insulin requirements to go up or down. It may increase uric acid blood levels, but has not precipitated or aggravated gout.

There have been no reports of toxic effects on the embryo. Female rabbits on nicotinic acid produced normal litters. A H referred to findings which showed that vitamin B3 could protect embryos from toxic effects of other drugs. Substances which prevent vitamin B3 from being incorporated into NAD are teratogens such as 6 aminonicotinamide. Nicotinic acid protects animals against these compounds. Mosher (1970) quoted these studies and had he found any evidence whatever for any teratogenic effect he would have certainly produced it. He concluded, "at this time there is little evidence either positive or negative with regard to the possible teratogenic effects of nicotinic acid." As he was unaware of the earlier report this is understandable. He subsequently apologized for his neglect to properly report the literature.

In a recent review Parsons (1974) discussed the side effects of nicotinic acid. He wrote, "Many clinicians are unduly concerned about the cutaneous flushing which niacin produces, apparently not realizing that with large doses it subsides early in treatment. Such negative attitudes have probably been enhanced by glib review articles listing symptoms and biochemical changes which occur during therapy, but failing to clarify which could be formidable." "It is also well to emphasize that the flush is at worst merely a nuisance which is not medically serious."

The committee writes, "Hoffer for example, in his 1967 pamphlet (18) and in his 1971 paper (13) cites violent vasodilatation. Here is what AH wrote, "Nicotinic acid produces a remarkable vasodilatation." The committee manages to transform remarkable into violent, evidence of bias which can hardly be lost on students of psychopathology. To round off this example they omit a description of how this flush recedes if one continues to take niacin.

In 1971 AH wrote, "It is still not clear how many of the gastrointestinal effects are due to the vitamin and how many to the vitamin filler." This is how the committee summarized it, "The gastrointestinal symptoms are attributed to the inert filler used in preparation of the B3 tablets." In this section the committee continues to distort both form and substance of what we wrote, presumably secure in the belief that their psychiatrist readers will not refer to the original publications. So far events have supported their belief. However, since they were entrusted by the APA to make an honest and unbiased report others may now become curious to see how they carried out a duty to which they were pledged both to psychiatry and to the public. This entire section on side effects reads like one of the glib reports with which Parsons takes issue. Regarding peptic ulcer Parsons wrote, "Although in 1960 I reported five patients in whom ulcers became active during niacin therapy subsequent experience has failed to show any close correlation." "I do not hesitate to prescribe niacin in a hyperlipidemic patient with previous ulcer."

With respect to liver toxicity highlighted by the committee, Parsons states, "Some of the serum enzymes used to assess hepatic function may be mildly to moderately elevated during therapy. These changes are usually not progressive, often returning to normal while treatment continues. Light microscopy has frequently shown no abnormality in

* emphasis ours, not in the APA report
hepatic tissue even when enzyme levels have been considerably abnormal. "Similar liver enzyme changes occur with clofibrate therapy and appears to be inherent in these drugs without signifying hepatic damage." Jaundice has been very rare.

About hyperglycemia Parsons wrote, the changes in carbohydrate tolerance have no clinical significance—unless the clinician incorrectly interprets them as evidence of diabetes." Discussing increased uric acid levels Parsons concluded, "Hyperuricemia occurs somewhat less frequently but has not been accompanied by gouty arthritis or renal calculi." Parsons found pigmented changes in the skin not significant. This he described as a localized velvety thickening and tanning of the skin especially in the axillae. This change, which resembles acanthosis nigricans, is of cosmetic importance only. It does not require that the drug be discontinued. Wittenborn et al. (1973) did not report any cases of acanthosis nigricans. They wrote, "A substantial portion of the sample developed a pigmented hyperkeratosis which in some cases bore a disturbing superficial resemblance to acanthosis nigricans." They referred to a report by Parsons. But it is obvious that Parsons who has been studying nicotinic acid since 1956 is not disturbed. It is not the tanning of the skin which is disturbing, but the unfamiliarity of Wittenborn and his colleagues with this phenomenon which excited and disturbed them. There are no reports that nicotinic acid causes acanthosis nigricans. The committee's statement was false when they wrote, "and acanthosis nigricans have been reported." From 853 patients treated with nicotinic acid for five years the Coronary Drug Project Research Group did not report a single case. They did not even mention it as a side effect.

The committee referred to a case of incipient psychosis produced by nicotinic acid. They apparently read a letter to the editor by Heninger and Bowers (1968) who concluded that 1% g of nicotinic acid produced a psychosis in a subject who had also been taking LSD, hashish, and a curious form of psychotherapy. The committee did not refer to a letter of rebuttal, from Hoffer (1969). Here he wrote "This pharmacologically naive report deserves little comment except that it will certainly be quoted widely as evidence for niacin toxicity." We did not then realize that a committee of the APA would be the first and only group to prove this prediction correct.

The committee's concluding paragraph on Page 44 of their report might be ascribed to a serious concern for the welfare of patients. But since every known tranquilizer is many times more toxic, one has to weigh the risks of: (1) Remaining chronically tranquilized and more or less ill for life. This as many authorities have indicated is occurring to an increasing number of patients with all the increasing risks of irreversible conditions such as tardive dyskinesia and akinetic mutism. (2) Recovering on the orthomolecular approach while using vitamins the rest of one's life. We believe that given such a choice and not misled by prejudicial comments most people would choose the latter. The risks are small. We have still to see a single patient harmed by megavitamin therapy although we have seen those not benefited. During the same time we have seen numbers of permanently impaired patients on tranquilizers. The costs in terms of their lives and to the community have not yet been computed, but they must be immense.

(22) Page 10, Attempts at Replication —The committee continues to insist that vitamin B3 is the crucial variable for the entire orthomolecular program. They use this to justify their single-minded employment of vitamin B3 in their experiments. This sometimes seems to be a deliberate attempt to confuse—one is unwilling to believe in such massive incompetence. Had Ban and Lehmann seen fit (as they had originally agreed) to repeat our original experiments using a combination of vitamin B3 and ECT, and had the results turned out negative, there is no doubt the committee would have dropped all reference to vitamin B3 as...
the crucial variable. No matter how the committee squirms about the issue, the fact remains that no one has repeated the original two double-blind experiments. Those who have employed the entire orthomolecular technique have become enthusiastic users.

(23) Page 11—The list of negative references on this page is interesting. Nowhere is there any reference in the body of their report to our first study where we showed that nicotinic acid alone did not help chronic patients (O'Reilly, 1955). O'Reilly was a colleague located at Saskatchewan Hospital, North Battleford. At our request he ran a study which was published in Diseases of the Nervous System. This was the first published account of lack of response of chronic patients. We have since then always made this clear as is evident from the review of our papers given earlier in this report. O'Reilly (1955) is reference #47 in the committee report. Then they refer to Ashby et al., who confirmed our report, and to Greenbaum who gave one-third the active dose to schizophrenic children. No information was given about the number who were cases of infantile autism.

The McGrath et al. report discussed 265 patients of whom 115 or 43 percent were ill five years or more, 91 (34 percent) were ill one to five years, and of whom only 59 (23 percent) were ill one year or less. Thus, only one-quarter were acute. This is then a study of the effect of nicotinamide on chronic schizophrenics. There is no breakdown anywhere in the paper between acute and chronic response to treatment. There is no evidence in this report to support the committee's statement 'no improvement was noticeable either after 30 days of treatment or after one year in either the acute or chronic patients' (McGrath et al., also confirmed O'Reilly, 1955).

The Wittenborn studies are reported in an interesting way. And since Dr. Wittenborn is introduced as an exceptionally experienced researcher in the area of drug effects on mental illness, it is especially important to examine carefully his "unusually comprehensive" studies not only for what Dr. Wittenborn himself must bear for the committee's report since he was the consultant. As with Ban the committee seems to be expert at mud-judging roles in a deplorable manner. We born the consultant.

We will list the Wittenborn conclusions and then the committee's interpretation when they are different.

Wittenborn et al. (1973) compared the effect of nicotinic acid, 3 g per day, plus tranquilizers against nicotinic acid alone on an experimental group of 47 ill, on the average 4.8 years against a control group of 28 ill. They found: (1) 24 percent from the vitamin group were dropouts and uncooperative compared to 37 percent of the control. This did not reach statistical significance, but suggests a trend for more cooperation among the vitamin group. (2) A slightly larger proportion in the nicotinic acid group remained in hospital each month. (This difference was not statistically significant. (3) There was no difference in the rate of readmission to hospital or in number of days spent in hospital. (4) There was no significant difference in number of patients requiring tranquilizers, or in the amount of tranquilizer required (dose). At the end of the first month, 87 percent of the vitamin group and 96 percent of the control group were receiving tranquilizers, while at the ends of 12 months these values were 77 percent and 89 percent. At the end of two years they were identical at 75 percent. (5) There was no significant difference between the two groups clinically. (6) Home and community adjustment was more favorable in the control group than in the vitamin group. (7) There were no cases of disturbed carbohydrate metabolism and gastroenteritis. (8) A number of patients developed a superficial pigmentation in their skin.

These findings were reported by the Yk committee except for their first statement: (1) Subjects on niacin tended to
stay in the hospital longer, but the statistical significance of this is uncertain. What Wittenborn et al wrote was that, "This difference continued throughout the course of treatment, but did not meet the criterion for statistical significance." There seems to be nothing uncertain about this last statement.

In a subsequent report (Wittenborn, 1973) first delivered in Washington and later published, Wittenborn (1974) reported that he had examined a smaller group of 24 patients selected on the basis of certain predictor indices. Half received nicotinic acid. Ten of the 12 patients in the vitamin group had outpatient adjustment scores of 0.60 or higher at 24 months, indicating a good outpatient adjustment score. In the control group, only five out of 12 achieved similar adjustment.

Wittenborn found "a high positive predictor score was associated with a clinically important advantage for those patients whose treatment comprised niacin supplementations." For depressive retardation, the percent of patients with substantial disorder at 24 months is approximately twice as great in the selected control group as in the selected niacin supplementation group. For schizophrenic excitement, the percent of patients with substantial disorder is more than twice as great in the control group at 12 and 24 months as it is in the selected niacin supplementation group.

Wittenborn (1973) stated, "There is a conceivable relationship between the fact that in the present sample patients with a high predictive score responded tell to niacin and the fact that Hoffer and Osmond had claimed that niacin was more effective in relatively acute patients than in chronic patients. It is probable that patients who, in the present sample, had a high positive predictor score would have been classified by Hoffer and Osmond as acute schizophrenics. Perhaps in this way the differential effect observed by them could be in part explained." Wittenborn further states, "those patients with conditions diagnosed as schizophrenic who come to treatment with a history of strong interpersonal commitments will respond well to niacin-supplemental therapy." This he proposed as a testable hypothesis.

The committee did not relish this second report and attempted to neutralize and obscure these findings by writing in their conclusion, "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." There is no evidence whatever for this simplistic mathematical conclusion. Had there been any subgroup identifiable in any way as a group made worse by vitamin B3, there can be no doubt Wittenborn upon the urging of the committee would have found it and reported it.

The committee referred to a possible one-quarter of the group who did well on vitamin B3 but neglected to refer to the 20 percent of the total group who were made worse on tranquilizers alone. Thus, Wittenborn (1974) wrote, "one possible explanation for the paradoxical persistence of symptoms in these control group patients with a good positive predictor score draws on observations that there are patients with a favorable premorbid history who may possibly be burdened by phenothiazine medication in their remission." He wondered if niacin might be antitoxic to the phenothiazines.

But this is how the committee summarizes it: "although Wittenborn considers his data to be consistent with the possibility that as many as one-quarter of his schizophrenic population (those with good premorbid adjustment) might be benefitted." We assume that this figure is derived by multiplying one-third (i.e., the number of subjects with good premorbid personality) by 10/12, i.e., the proportion who responded to nicotinic acid plus phenothiazines. Note that the committee in criticizing our work never talks about nicotinic acid and ECT in the same sentence, but here they want to leave the suggestion it was the phenothiazine which should be
emphasized. This may be how the committee arrives at the one-quarter estimate.

Wittenborn in his papers does not make this sort of calculation. In our opinion, Wittenborn had discovered unusual and one might think unnecessary criteria for selecting Phase I patients. The proportion of Phase I patients, i.e., acute or less serious cases, varies with the sample. Thus, from a cohort of schizophrenics seen for the first time in outpatient clinics or by psychiatrists in private practice a much larger proportion are early, less serious, or Phase I. From a cohort admitted to a mental hospital a much smaller proportion are Phase I. Out of one practice in Saskatoon about 50 percent are early and AH is the first psychiatrist they have seen. The other half have been to one or more before and are not apt to be Phase II. Since going to a mental hospital very often means that there is no other facility willing or able to take the patient they are more chronic, have already failed to respond to treatment, and are generally more intractable. It is, therefore, not surprising to find only one-third of the Wittenborn group were Phase I. But to be fair and objective the committee might have abstracted Wittenborn's paper more carefully. Even so, there is no evidence from the Wittenborn studies that the two main groups were suitably identical since the placebo group were 1.8 years less chronic (4.8 compared to 3.0). A substantial fraction of the poorer prognostic vitamin group could have responded without any significant difference appearing, and a substantial proportion of the better prognostic placebo group might have responded had they been treated with nicotinic acid. Thus, the one-quarter estimate is so crude as to be trivial.

In other words, Wittenborn's study confirms our claims that a substantial fraction of schizophrenics, i.e., Phase I, will respond to nicotinic acid without ECT. But we must emphasize that this is seldom our recommendation today. The committee quibbles on the proportion in Phase I. Even if we accept their estimate of one-quarter based upon a mental hospital admission cohort, this is still appreciable. Having admitted that one-quarter might be benefited the committee, by a form of convoluted reasoning which is very mysterious, states, "the fact that he finds no significant difference between the total control group and the total vitamin group implies a fraction of his experimental population may have had their progress impeded by the vitamin addition." One could just as well argue that there has been a simple placebo versus niacin study omitting tranquilizers; the results might have been even more significant in favor of vitamin B3.

Wittenborn tried to save his study from becoming too much in favor of niacin by suggesting that the 35 percent of his total group were not really schizophrenic. If this suggestion is accepted seriously, then the whole study must be in jeopardy. For who would give a moment's consideration to an investigation in which the chief scientist reports that one-third of the patients did not have the illness being studied?

The committee totally ignored DeLiz's (1973) charge that the Wittenborn study did not maintain its double-blind status. Although Wittenborn maintained it was double blind, he presented no evidence that it had remained so. There were no questionnaires for either patient or staff to determine whether they thought they were getting niacin or placebo. DeLiz stated that some patients were aware; they were on placebo and at least one purchased his own niacin. This is not to be construed as an attack on Wittenborn who is an able research worker, but on the methodology of the double-blind technique. It requires an al super human effort to insure the double-blind is not broken.

In the Wittenborn studies it would have been impossible to insure it remained double blind because of the vasodilation. He attempted to cover this by starting the entire group on 50Q milligram tablets to give them all the flush and then changing the placebo group over to placebo. But any of these
any experience with long-term niacin use knows that now and then throughout treatment there will be random flushes, usually after the first dose in the morning. We suspect that after a few months nearly every patient on niacin will know he has flushed and most of the group will know why.

Furthermore, a number of patients who developed pigmentation had their medication decoded and after a while were restarted on the niacin. Thus, the double blind was not maintained through no fault of the investigators (De Liz, 1975; Adams et al., 1975).

We now come to the Canadian Mental Health Association’s studies begun with a grant given to Dr. T. Ban. The reason the CMHA did this was that they became disturbed by the claims that adding vitamin B3 to the treatment program doubled the recovery rate. They instructed Dr. Ban to disprove once and for all time our claims. One of us (AH) that year was on the Scientific Advisory Council and was familiar with the background. When Ban’s initial design was seen it was obvious he was prepared to use only Phase I treatment, i.e., no ECT. When this was pointed out to him he responded with the reassuring statement that after their first researches were completed they would continue with Phases II and III. He also added there would be no release of any information until the entire program (Phases I and II) could be completed. It now appears that he had no intention whatever of going beyond Phase I treatment for all patients and, as events showed, he rushed into print very soon after the first study was completed. He was supported by CMHA who circulated his first report to every psychiatrist in Canada. They have since refused to correct the misinformation distributed therein, claiming they cannot be involved in any treatment controversy.

Examination of Table 1 of the committee report shows no evidence whatever of any study repeating any of our original double-blind studies (vitamin B3 and ECT as required).

For each of their published studies we will abstract what the authors wrote and this will be followed by the committee’s abstract.


In this study they treated 30 newly admitted schizophrenics. They do not describe them as acute or chronic, but as newly admitted. This is an interesting term and suggests that the patients were acute. Anyone familiar with the Douglas Hospital in Montreal knows that newly admitted patients there include a large proportion of chronic cases, many of whom had failed to respond to treatment in a number of psychiatric wards in general hospitals. The words newly admitted have no meaning whatever and the authors would have been more honest to have simply called them admitted schizophrenics and to have described their sample more carefully.

Hoffer (1974) investigated these studies carefully and wrote, “The patients were divided into three groups, one group receiving nicotinic acid, one group nicotinamide, and the third group placebos. Neuroleptic tranquilizers were administered to all the groups on a restricted scale. It was intended to investigate the patients for two years, but only six patients completed the entire period. Nevertheless, 25 patients spent the first three months in hospital and at the end of this period their clinical status was assessed by means of the Brief Psychiatric Rating Scale (BPRS).”

“It was found that there were statistically significant improvements in the total BPRS scores for all three groups. However, Table 3 of the research paper shows that out of 15 BPRS items, the patients receiving nicotinic acid improved in 11 items and the patients receiving nicotinamide improved in 12 items, while the patients receiving placebos improved in only six items. Thus, both the B3-treated groups scored improvements in approximately twice as many items of the BPRS as the placebo-treated group. The published paper also includes clinical assessments of the
patients at the end of the two-year study. There were improvements in 10 out of 15 items in both the nicotinic acid and the nicotinamide-treated groups, but improvement in only six items in the placebo-treated group. Because 80 percent of the patients dropped out of the study before its completion, these results are much less reliable than the ones obtained at the end of the three-month period in hospital, when few patients had dropped out. However, the same general picture is obtained as at the end of the three-month period; that is, both the nicotinic acid and the nicotinamide-treated groups improved in many more I3PRS items than did the placebo group.

The committee reports, however, "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—3,000 to 8,000 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 clays) 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 (188).

J Hoffer then properly concluded, "The summary of this study given in the Task Force Report doesn't mention these results. Instead, it points out that the average number of days in hospital during the two-year period was 211 days in the placebo-treated group, 214 days in the nicotinic acid-treated group, and 353 clays in the nicotinamide-treated group, showing that the length of time spent in hospital was not significantly different for the B3-treated groups compared to the control group. The conclusion to be reached about the study depends on whether one takes the average number of days spent in hospital as the critical variable, or whether one takes the number of symptoms of mental illness alleviated in the course of the treatment as the critical variable. The latter is by far the more reliable.

"The Task Force Report has interpreted this study as demonstrating that (page 15): '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.'

"This conclusion is based on the insignificant differences in average duration of hospital stays. The evidence derived from actual psychiatric evaluation of the patients, which showed a definite superiority of both the groups receiving B3 over the control group, is not even mentioned."

CMHA Study No. 3 (No 53 in bibliography) from J Hoffer:

"The Task Force Report summary of the CMHA Study No 3 by Ramsay et al. (53) also gives a false representation of the actual findings. On Page 15 the Task Force Report states:

"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 3,000 mg per day, to the regular phenothiazine treatment prolonged the duration of hospital stay and increased the amount of neuroleptic medication required in treatment."

"The results of this study," J Hoffer concluded, "do not show that patients receiving nicotinic acid were made worse, because of it. The difference in the average duration of hospital stays was not significant. The difference in the average amounts of neuroleptic tranquilizers administered to the different groups is of doubtful significance. The
drugs were prescribed for more than half the duration of the study on the basis of short, outpatient interviews by resident psychiatrists (psychiatrists in training). Even among experienced psychiatrists, the dosages of these drugs given to acute schizophrenics are highly variable. The dosage of a tranquilizer drug prescribed for a psychotic patient is a very crude and very indirect indication of his clinical status, and it can be influenced by a multitude of extraneous factors.

"The direct and obvious method of assessing the condition of patients is by observing them. If B3 had worsened the patients, it would be detectable by a worsening of their symptoms. In fact, it was found that the B3-treated groups improved significantly. The research paper states:

Of the three, the nicotinamide-treated groups showed statistically significant therapeutic improvement on more individual items (9) of the BPRS than either the nicotinic acid or the placebo groups: the latter two groups showed significant improvement on six and eight items respectively (53)."

One may conclude that the B3-treated groups in this study did not, in the overall assessment, improve more than the control groups. This has little relevance to orthomolecular therapy, in which 133 would not be used alone and in such small dosages. There is no evidence that 133 worsened the condition of the patients who were treated with it.

Contrary to the findings of an increased need for tranquilizers, Wittenborn found no significant difference in tranquilizer requirements, nor did he find any difference in the number of days in hospital. Thus, Wittenborn demolishes two of Ban's main criteria of improvement. Ramsay et al. did not report any mean HOD scores, but did report mean MMPI scores (only 11 out of 30 were able to complete MMPI). Half the group completed the HOD. Had they given HOD scores perhaps some differences might have appeared. Since as a rule they downgraded positive responses, one is left with the assumption there may have been something there. The fact that only half were able to do the HOD suggests these newly admitted patients were a very chronic group. In Saskatchewan only chronic patients incarcerated for many years had this low a completion record on the HOD test. Acute and subacute cases never had more than a 5 percent rate of not being able to complete the HOD.

CMHA Study No. 4 from J Hoffer:

"The final CMHA collaborative study was conducted on 30 chronic schizophrenic patients. In this study one group of patients was treated with 3 g of nicotinic acid, one group with 3 g of nicotinamide, and the third group was given placebos. The Task Force Report's summary of the results of the study is as follows:

"From Study No. 4: the overall therapeutic efficacy of nicotinic acid—in the dosage of 3,000 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.

"The actual published data shows that every statement in this summary is false. In the study, three methods of clinical evaluation were used: the Clinical Global Impression Scale (CGI), the Nurses Observation Scale for Inpatient Evaluation (NOSIE), and the Brief Psychiatric Rating Scale (BPRS). The patients were rated on these scales before the study began and after its conclusion, and the results are these: the changes in all three evaluation scales before and after treatment were insignificantly small for the
patients in the two B3-treated groups and in the placebo group. There was no improvement and no deterioration in any group.

"It is clear that a treatment of 3 g of B3 per day did not benefit these chronic patients. This is a result to be expected on the basis of the studies by Dr. Hoffer and Dr. Osmond and by Dr. O'Reilly, who had already reported that chronic patients, like the ones in this study, do not respond to 3 g of B3 alone. At the same time, contrary to the claims in the Task Force Report, there is absolutely no evidence that the administration of B3 worsened the condition of the patients who received it. It can easily be shown that the numerical variations in the clinical scales which were observed are small, random fluctuations which are due to the inexactness of the evaluation methods. For example, on the CGI scale, the nicotinic acid-treated group went from a pretreatment score of 4.1 down to 3.9 after treatment, an improvement of 0.2 points. The placebo group went from 4.2 down to 3.7—an improvement of 0.5 points. The nicotinamide group also improved by 0.5 points (4.7 to 4.2). On the basis of this the Task Force Report states that the nicotinic acid group had the least improvement and the greatest amount of deterioration. Yet the CGI scale in this experiment is inexact by a minimum of 0.6 points; any change less than that is equivalent to no change at all. The nicotinic acid group's 'improvement' by 0.2 points is not less than the placebo and nicotinamide groups' 'improvement' of 0.5 points—all these changes are too small to have any significance.

"The Task Force Report states: 'the active treatment groups fared worse than the placebo group by all measures of assessment.' This is false for the nicotinamide group 'improved' on the BPRS by 1.3 points (improving from a pretreatment score of 45.2 to 43.4 after treatment), while the placebo group 'deteriorated' by 1.6 points (rising from 37.8 to 39.4).

"As it happens, BPRS was imprecise by at least 10 points, so these changes, too, are not significant. The differences in the average dosages of the tranquilizers administered to the patients before and after treatment were also insignificantly small. There was no evidence that the patients in the placebo group required less increase in their tranquilizer medication than the B3-treated patients; the statement to this effect in the Task Force Report is wrong."

In APA Bibliography #56 Ban and Lehmann also reported on 10 newly admitted patients (acute and subacute is given as a descriptive term, but no data is given on their chronicity) Three were on nicotinic acid, three on nicotinamide and four on placebo. In this study the nicotinic acid group required 164 mg tranquilizers/day and the placebo group 259 mg per day. However, they downgrade this by promptly pointing out the placebo group had fewer days in hospital. Neither of the indices has any value in judging response to treatment. There are too many clinical variables in our own studies we never used duration of first treatment admission as a criterion, but we did use duration of readmission as a measure. Ban and Lehmann studiously avoided this latter statistic. They can conclude, it would be erroneous to amplify results of our clinical trials with other negative reports and to conclude that nicotinic acid has no place in treatment of schizophrenic patients. This was one of their few correct statements, especially its first part, based upon 10 patients in one study and 30 in another. Then they continue with the meaningless and trivial statement, all one can say on the basis of these findings is that there is sufficient evidence to suggest strongly that, nicotinic acid or nicotinamide is not the treatment of choice for every schizophrenic patient under all possible conditions and without any further consideration. Is there any drug used for any condition for which this statement would be untrue?

This statement was repeated by Dr. J. D. Griffin, General Director, Canadian Mental Health Association (Progress Report 1). Since then and following his retirement, Mental Health Canada has
changed its position and no longer officially wishes to be involved in the continuing controversy.

Study No. 7, from John Hoffer, page 26:
"Study No. 7 of the CMHA studies by Ananth, Ban, and Lehmann, 1973, is entitled 'Potentiation of Therapeutic Effects of Nicotinic Acid by Pyridoxine in Chronic Schizophrenics.' It was intended in this experiment to test the finding of orthomolecular psychiatrists that B3 and 136 (pyridoxine), when combined, have an enhanced effect in the treatment of schizophrenia. A 48-week double-blind study was conducted in which one group of patients received nicotinic acid, one group pyridoxine, and a third group received a combination of nicotinic acid and pyridoxine. All the patients were chronic schizophrenics. The Task Force Report summarized the results of this study as follows (page 15):

"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.'

"This summary is a completely inaccurate description of the actual findings in the study. The results which were actually obtained and reported in the published research paper were the following:

"In this 48-week placebo-controlled study, the therapeutic effect of a combination of nicotinic acid and pyridoxine was compared with that of treatment with either nicotinic acid or pyridoxine alone. Of the three indices of therapeutic effects, global improvement in psychopathology (BPRS and NOSIE) scores was seen in all three groups; the number of days of hospitalization during the period of the clinical study was lower in both the nicotinic acid and the combined treatment group; and only in the combined treatment group was the daily average dosage of phenothiazine medication decreased. Thus, improvement in all three indices was noted in the combined treatment group.'

"And:
"'On balance, these results suggest that the addition of pyridoxine may potentiate the actions of nicotinic acid. Thus, pyridoxine seems to be a useful adjunct to nicotinic acid therapy.'"

Study No. 12, from John Hoffer, pages 24 and 25:
"First, Study No. 12, by Ananth, Ban, Lehmann et al. is entitled, 'Nicotinic Acid in the Prevention and Treatment of Artificially Induced Psychopathology in Schizophrenics' (54). It consisted of a study on chronic schizophrenics (Phase III) in which half the patients were given nicotinic acid in a dose of 3 g per day and half were given placebos, for two weeks. The neuroleptic tranquilizer therapy which all the patients had been on was withdrawn. As might be expected, the patients receiving placebos deteriorated significantly when the tranquilizers were withdrawn. However, the patients receiving 3 g of B3 showed a marked statistically significant improvement.

"All the patients were then given very large doses of methionine, 20 g per day, along with their continued medication of 3 g of B3 or placebos. The hypothesis tested in this experiment was that methionine, which has been shown to worsen the symptoms of schizophrenia, might exert this effect because it is a methyl group donor. B3, on the other hand, is a methyl group acceptor. It was hypothesized that the effectiveness of B3 in schizophrenia results from this characteristic of the molecules of B3; that is, B3 might remove methyl groups from some methylated compounds in the body which could be causing the mental illness.

"After the administration of 20 g of methionine per day, all the patients showed a pronounced worsening of their symptoms. The Task Force Report has interpreted this as showing that nicotinic acid does not neutralize the methyl-donating effect of methionine in worsening schizophrenia. This conclusion, however, is not justified, because there was a serious flaw in the experiment. The patients were given 20 g
of methionine per day, but only 3 g of nicotinic acid. Over 16 g of nicotinic acid is required to accept the methyl groups donated by 20 g of methionine. The experiment was bound to fail.

"This flaw was acknowledged in the original published research report as well as in an official summary of it. The flaw is not acknowledged or even mentioned in the Task Force Report. The only valid finding emerging from this study is that B3 not only forestalled the deterioration anticipated when tranquilizer medication was withdrawn, but it produced a significant improvement in the patients treated with it. This finding is not mentioned in the Task Force Report."

Methionine binds pyridoxine which is essential for the conversion of tryptophan into coenzyme one, nicotinamide adenine dinucleotide (NAD). The injurious effect of methionine is therefore easily explainable. It would be almost a miracle if any quantity of vitamin B3 could compensate for a methionine-induced pyridoxine deficiency.

J. Hoffer therefore concluded (Page 28):

"In summary, three of the five CMHA studies provide evidence to support the findings of orthomolecular psychiatry. The Task Force Report's description of every study is biased and misleading. It is remarkable that the authors of the report make incorrect claims that B3 is worse than a placebo, putting the most negative possible interpretation to some equivocal research findings, while not even mentioning the research findings that showed B3 was of clear definite benefit."

Recently, one of us (AH) criticized Ban (1975) for repeating his claim that nicotinic acid did not protect patients against toxic doses of methionine. In his reply, he produced a new objection claiming that patients on a combination of nicotinic acid plus methionine and the amine oxidase inhibitor deteriorated more. The following letter was submitted to the Journal of Psychosomatics, but they did not want to publish it as they did not wish to continue the controversy. Apparently the editorial board believed they had already given too much space to orthomolecular psychiatry.

"Sir:

"In a recent reply to my letter, Ban (1975) has retracted his earlier conclusion 'Nicotinic acid failed to prevent by prior administration or to relieve by subsequent administration the methionine-tranylcypromine-induced exacerbation of psychopathology.' (Ananth et al., 1970, Canadian Psychiatric Association, 15, 15-20, 1970) He had in the body of the paper recognized that 3 g of nicotinic acid was totally inadequate to counteract any methyl-depleting effect which could be ascribed to methionine. But having recognized this he should have concluded that his experiment was irrelevant and trivial and added nothing whatever one way or the other to any methylation hypothesis. However, Ban finds it very hard to admit he has erred and attacks the problem from another direction. Although this recent idea of his does not appear anywhere in his original paper, he now concludes that nicotinic acid had a negative therapeutic effect on the two toxic drugs he had given his patients in large dosages."

It is interesting to read again his original paper. This I urge every reader to do. To help them follow the reasoning of his earlier work I have subjected his paper to a critical scientific look.

In this paper, 20 chronic patients were divided into two groups of 10 each. The 10 destined to receive nicotinic acid consisted of seven men and three women. The control (placebo) group consisted of three women and seven men. This immediately shows that his randomizations had broken down and that the experiment no longer met the rules of double-blind methodology. The whole experiment should have been scrubbed, especially by a group so keen on methodology as Ban and his colleagues. In effect, the nicotinic acid group were male and the placebo group female.

In his introduction he ascribed to us-
incorrectly that we tested a hypothesis that nicotinamide would prevent excess methylation. In fact, the hypothesis we tested was that the addition of vitamin B3 to the current treatment program (then ECT and psychotherapy) would improve the outcome, and it did. We then described a large number of hypotheses to explain how it could work, and the methylation idea was one of them. It was also one of our ideas (among a number of others) which led to our first pilot trials in 1953. These preceded our double-blind experiments in 1953 to which Ban makes no reference. He leads the unwary reader to believe we did not do double blinds. We were the first psychiatrists ever to do them as is clear from our 1957 paper to which Ban refers.

Then Ananth et al. (1970) claim their experiment was double blind. It was not. It is impossible to double blind any study with nicotinic acid as any physician who has used it knows. The initial dramatic flush usually (but not always) recedes and is seldom troublesome, but nearly every patient on maintenance medication even for many years will flush now and then, especially in the morning with the first dose. The flush is unmistakable by the flusher and anyone who sees it. Therefore, it cannot be double blind. In our first experiment we used three treatments, placebo, nicotinamide, and nicotinic acid in conjunction with ECT if needed and with psychotherapy. No one in the unit knew that nicotinamide was included and as it does not produce a flush it was not detected. This, then, was a true double blind.

Ian is well aware of the fact that you cannot blind nicotinic acid because in his first unpublished protocol he called it a semi-blind experiment. No matter what he called it, it was not blind, nor was any evidence published that it was. It is strange that in studying the effect of toxic quantities of methionine he did not use a placebo comparison.

After a two-week drug wash-out period, the male group were placed on nicotinic acid and the female group on placebo. Out of the male group (on nicotinic acid) eight improved and two deteriorated (P < 0.02). Out of the female group, six deteriorated and two improved (There is however some confusion since these figures do not agree with Table 3 nor is it clear which scale is being used to evaluate response) (P < 0.05).

It is clear that in a group of mostly male chronic schizophrenics who needed neuroleptic drugs all the time* (quotation from Ananth et al.) nicotinic acid not only prevented a relapse, but produced an improvement. They had not reported for these patients on neuroleptics only. The placebo group deteriorated as one would expect.

For the next two weeks the entire group were placed on the amine oxidase inhibitor tranylcypromine, 30 mg per day. But there is nothing in the report to indicate what happened to the patients. For the next four weeks all the patients were placed on 20 g of methionine per day.

But according to Ananth it was maintained for one week in six patients and for two weeks in another four. That is, half the group were dropped out before completing the four weeks. This means (also not mentioned by Ananth) that the same 10 were no longer on the amine oxidase inhibitor. Nowhere is there any indication which group, the nicotinic acid or placebo group, had the greatest number of dropouts. Therefore, any meaningful evaluation is probably impossible.

The last period of four weeks the original male nicotinic acid group were switched over to placebo while the original placebo female group were started on nicotinic acid.

In the female group (on nicotinic acid for the first time) the deterioration started by placebo at the beginning of the study and intensified by toxic doses of methionine was not reversed by nicotinic acid.

Seven patients continued to deteriorate and three improved. From the original male group (on nicotinic acid) the original improvement caused by nicotinic acid and reversed by toxic doses of methionine was not reversed by
placebo These results are shown in the following table taken from Ananth's own results:

<table>
<thead>
<tr>
<th></th>
<th>worse</th>
<th>no change</th>
<th>better</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Patients originally on vitamin B₃ and finally an placebo</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>b</td>
<td>Patients originally on placebo and finally on vitamin B₃</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

It seems to me that these groups are not significantly different in terms of their response to placebo and nicotinic acid. However, Ban writes, "Furthermore, it was noted that after discontinuation of both tranylcypromine and methionine administration there was deterioration with nicotinic acid and some improvement with placebo within a two-week period." "It is this negative therapeutic effect of nicotinic acid and not the lack of prevention of methionine-induced exacerbations in schizophrenic patients that we keep on stressing, something which Dr. Hoffer systematically and consistently chooses to ignore."

In other words, Ban bases his entire case on the fact that with nicotinic acid (given to the original female placebo group), seven were made worse while in the other group only six were made worse and one showed no change.

Is there any reason why this finding should not be ignored? Had the one patient changed from none to deterioration the results would have been identical.

Finally, Ban ignores the fact that methionine binds with pyridoxine and produces a pyridoxine deficiency. This would be worse the longer patients remained on the amino acid. Why would anyone expect vitamin B₃ to compensate for a vitamin B₆ deficiency induced by methionine?

Beaton et al. (Biol. Psychiatry 10, 45-52, 1975) found that methionine decreased REM sleep in rats and mice which was not reversed by nicotinamide. Their experiment suggests that methionine does not increase methyl groups, but that the effect is due to a metabolite of methionine-homocysteine. We have, therefore, two possible ways by which methionine is toxic. Yet Ban continues to use his early study as an argument against vitamin B₃ as a therapeutic agent for schizophrenia.

The only reasonable conclusion from his entire paper is that it was poorly conceived, badly executed, poorly reported, and faulty in its conclusions. As I have said earlier, it is irrelevant and trivial to the orthomolecular controversy and serves only those who refuse to read the original papers pro and con and who prefer to be led by authority and not by scholarship.

The table on page 31 details the treatment, patients, and indices of change used by Ban and Lehmann and those we used.

Yet the committee can write, "The negative findings in these carefully controlled studies are clearly at variance with results claimed by megavitamin proponents." It would be surprising indeed if the Ban-Lehmann studies could have come to any other conclusion since they used chronic patients mostly (even if newly admitted) without ECT for those for whom it was indicated and did no follow-up studies.

Had we done our original studies the way Ban-Lehmann did we would have undoubtedly come to their conclusions.

It should also be made clear that even though they claim their studies were double blind (Ananth et al., 1973), it is impossible to keep a patient on nicotinic acid unaware of the fact he flushes now and then and equally impossible to prevent nurses or other staff from seeing the flush when it does occur. Thus they are on weak ground and most often refer to placebo-controlled studies, thus lulling the unwary reader into believing these studies were double blind. In our first double blind we used nicotinamide as a hidden control, i.e., no one knew it was being used. In our second study we did not use it, but told everyone we were including it. Thus our placebo and nicotinamide groups were true double blinds and the second was also by inference No attempt was made...
in these studies to make them really double blind. Finally, they presented no evidence that the code had not been broken by patients or staff, something surely that no modern double-blind methodologist would fail to do.

In a recent report Ban and Lehmann (1975) caution physicians against the use of these dangerous vitamins invoking the Hippocratic oath, primum non nocere. This is rather surprising when one reads their report #12 wherein they showed that schizophrenic patients who were improved by nicotinic acid were then given a combination of a monoamine oxidase inhibitor plus a toxic dose of methionine, 20 g per day, and so made worse. One wonders about the ethics of workers who in the name of science allow patients to be made worse while trying to frighten physicians away from a vitamin considered safer than any tranquilizer presently available. When we recall the cases of tardive dyskinesia, jaundice, incapacity to function, obesity, and other toxic changes produced by tranquilizers we are delighted we have only to deal with a few cases of nausea, flushing, and so on produced by vitamin B3.

Claude Bernard emphasized in clinical experiments activities likely to harm and unlikely to help are by definition excluded. In the Canadian experiments of Lehmann and Ban this simple condition was omitted and the omission was so flagrant as to throw doubt on the good sense, the fairness, and even the humanity of the experimenters. This occurred most obviously in the experiment where chlorpromazine was withdrawn and the patients were placed on niacin. At the end of the period of this phase of the investigation those on niacin had improved and those on placebo had become worse. The ethical experimenter would then have given those on placebo niacin which was exactly what we did in our second niacin double-blind study. Failure to do this was...
scientifically unsound for more information would have been gained this way, and morally inept. What Lehmann and Ban actually did was scientifically idiotic and morally reprehensible. It is inconceivable that their mentally ill patients would have agreed to their second stage had they been in their right minds. We do not believe their relatives would have agreed and no legal guardian could possibly have consented. If the Canadian Mental Health Association associates itself with such an experiment then public support should be withdrawn.

What happened was this. The patients who had been improved by the minimal (3 g) doses of niacin even though their tranquilizers had been withdrawn were given 20 g a day of methionine. There was ample evidence that this amount of methionine made many schizophrenics worse and there was none that any had been benefited by it. Under Bernard’s rules it was a disallowed experiment. However, as Linus Pauling has emphasized even supposing one ignores the ethics of the experiment and can separate them from its scientific value, this was scientific nonsense. The 3 g of niacin were substituting very successfully for the withdrawn chlorpromazine, but there was no reason to believe it could possibly cope with 20 g of methionine. It says much for the ethical insensitivity and scientific obtuseness of the APA Task Force that this reprehensible experiment seems to be well accepted by their committee.

In their earlier reports Ban and Lehmann were convinced that the inability of 3 g of niacin to reverse 20 g of methionine disproved a transmethylation hypothesis and so removed a theoretical rationale for the efficacy of vitamin B3. They no longer follow this line of reasoning, but maintain that the niacin aggravated the toxicity of methionine compared to placebo. An examination of their published data does not support their conclusion. There appears to be little difference for methionine with tranylcypromine was toxic with or without niacin.

There are several means by which methionine could make patients worse:
1. By binding pyridoxine and producing a deficiency of this vitamin,
2. By increasing homocystine.

Thus, Beaton et al (1975) found that methionine produced behavioral and sleep cycle disturbances in rats and mice, which were antagonized by L-serine but not by L-histidine or nicotinamide. Apparently an increase in methyl groups was not a factor. In their experiments, nicotinamide increased rapid eye movement sleep in contrast to methionine which decreased it.

We still believe the transmethylation idea is worth examining although it is likely to be only one possible factor. It was first proposed by Osmond and Smythies (1952). Kety (1967) was interested in this hypothesis, but it always seemed to bother him that no transmethylation hypothesis can ignore vitamin B3. However, with a simple stroke of the pen, Ban and Lehmann (1975) have solved this problem for their colleague who is equally determined never to allow additional adequate clinical trials to be carried out by establishment centers. Ban et al, state, in 1967 Kety formulated the trans-fmethylion hypothesis of schizophrenia by shifting the emphasis from the psychotoxic compound produced by f' faulty transmethylation to the biochemical process itself. By this they hope to entrench Kety as the originator of the transmethylation hypothesis. However, to a biochemist, this statement by Ban is meaningless. The object of any biochemical reaction is the transformation of one molecule into another. Only, a molecule can be harmful, not the process of its formation.

Pellagra, Schizophrenia, and the Question of NAD

The committee as usual finds that speculations offered in 1957 for the theme action of vitamin B3 are contradicted by other hypotheses considered 13 years later. In fact, no one knows why vitamin
The argument that schizophrenia and pellagra are not identical is spurious. There is a wide overlap. Many pellagrins in southern mental hospitals were confused with schizophrenia, and around the turn of the last century the differential diagnosis included pellagra and dementia praecox. This is reviewed in a chapter in *Orthomolecular Psychiatry* (1973) which the committee did not read (at least they did not refer to it in their long polemic). See also Hoffer (1970). There is no doubt that pellagra produces a schizophrenic syndrome.

The committee then zeros in on our nicotinamide adenine dinucleotide (NAD) studies. First, they point out no studies have ever been published relating NAD blood levels to schizophrenia. But they then fail to add that the relationship between blood NAD levels and pellagra is not good. There are two main nucleotides: (1) the mononucleotides which are inactive as enzymes and (2) the dinucleotide. In pellagra even though total nucleotides are in the normal range, there is a significant increase in the mononucleotide fraction. There are no studies showing how these substances are distributed in schizophrenic red cells. Unpublished work by Philpott (1973) does show that schizophrenic erythrocytes in many patients are lower and that a vitamin B3 treatment improvement coincided in time with restoration of normal total nucleotide levels. We would expect that schizophrenic red cells contain too much mononucleotides and too little of the dinucleotide, NAD. This has yet to be examined.

Secondly, they state that NAD cannot penetrate into cells on a priori grounds. Most scientists know that even the best a priori reasons must give way before the facts. Apparently, Ban was once aware of this since in 1970 he wrote, "In spite of the challenging theoretical considerations based on animal pharmacological studies and Hoffer's (1966) positive therapeutic results, the unsuccessful attempts to replicate his findings have resulted in a decrease of interest in the nicotinamide adenine dinucleotide question."

The NAD problem was brought into a different light, however, by the systematic studies of Pfeiffer and his collaborators (1968). In combining the clinical with the electroencephalographic method, Pfeiffer and his group were able to demonstrate that an enteric coated NAD preparation does exhibit a therapeutic action. Pfeiffer et al.'s (1968) findings indicate that the claims about the clinical effectiveness of NAD therapy need to be further investigated with contemporary methods.

Recently, Liebow and Rothman (1975) reported that intact digestive enzymes can be absorbed by the intestine and resecreted by the pancreas. They specifically studied chymotrypsinogen, a very large molecule, much larger than NAD. They further report that the intestinal epithelium is permeable to a variety of proteins and they list a number of references for this observation beginning in the year 1958. If such a large molecule can pass through the intestinal cell walls intact there is no reason why NAD, a much smaller molecule, should not pass through. And if it can pass through into a cell there is every reason to believe it can pass into other cells also as needed. The problem is to place NAD far enough into the intestine to avoid the enzymes of the stomach and the upper part of the small intestine. This is why special preparations must be used.

Thirdly, they falsely state that the NAD studies we published were thoroughly refuted by several groups. We will now show what we did and what these other investigators did.

**Our Studies**

We used a number of acute and chronic schizophrenics, not chronic patients only as the committee stated. Our exact words were, "In this study NAD was given to a wide variety of schizophrenic patients who had been ill from six months to 30 years."
This study was done at University Hospital, Department of Psychiatry, Saskatoon, Saskatchewan in 1966. One patient had been transferred from a mental hospital, Miss A N., the rest were either inpatients or outpatients. None had been chronically incarcerated in mental hospitals even though they had been ill for a long time.

The NAD was a specially prepared enteric tablet in an oily medium. The contents were designed not to be released for two—three hours after they were swallowed. We found that out of 18 patients, six were much improved and two improved before receiving NAD, 11 became well in a few weeks (some in a few days), three much improved, and four improved. When we ran out of supplies of NAD within a few weeks all the patients reverted to their earlier state. Miss A. N., as we reported, was remarkably improved and this was witnessed by the psychiatrist who had known her best, Dr. M. Herjanic. As long as she was on NAD, she remained well. When we ran out, she relapsed. There was never any improvement thereafter even for a day until she died in the mental hospital a few years later.

We thus used a specially prepared NAD on a variety of acute to chronic cases of whom only one had been a chronic mental hospital schizophrenic. There were a few studies where the authors tried to test out NAD. The first one was a study by Kline et al. (1967). Kline used a number of chronic patients who had been in the hospital for many years. The committee conveniently leaves the word chronic out even though Kline had it in the title of his report. Kline also used his own preparation of NAD which was impure and which could hardly have survived passage through the stomach. Although the committee referred to HOD tests, Kline, in fact, did not accept the conclusions of the HOD which showed that the four patients on NAD had marked decreases in HOD paranoid, perception, and total scores while four patients on placebo showed no decrease in HOD scores. Pfeiffer found that Kline's preparation showed very slight activity on the quantitative EEG compared to our preparation. Gallant et al. used the same NAD, but as he stated used a group of chronically incarcerated patients. The other three if studies are irrelevant since we did not use IV NAD. Thus, it is clear that so far no one has used the same two factors as we did, i.e., (1) a good preparation of NAD, (2) a group of acute and chronic cases who had not been chronic inmates of mental hospitals. They were typical psychiatric ward patients commonly admitted to general hospitals in 1966.

The differences in the studies are shown in the following table:

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffer and Osmond</td>
<td>a special commercial preparation</td>
</tr>
<tr>
<td>Kline</td>
<td>his own preparation</td>
</tr>
<tr>
<td>Gallant</td>
<td>same as Holler</td>
</tr>
<tr>
<td></td>
<td>acute and chronic, not chronically incarcerated</td>
</tr>
<tr>
<td></td>
<td>in mental hospitals</td>
</tr>
<tr>
<td></td>
<td>chronic mental hospital patients</td>
</tr>
<tr>
<td></td>
<td>chronic mental hospital patients</td>
</tr>
</tbody>
</table>

In our report (1966) in reply to Kline we wrote, "Because NAD is hydrolyzed readily by phosphatases in the digestive tract, NAD given orally probably will be inactive unless it is prepared in a special form that will carry it into the intestine, where this destruction is minimized. In the research reported in 'Enzymology of Hallucinogens' the material was suspended in a special vehicle and encapsulated in a heavy enteric coat, Canadian Patent #670, 909—1963. It was released; two to three hours after being swallowed. Earlier studies by Enzomedic Laborator had shown that this preparation was active in many patients when unprotected NAD was not active. "Since 'Enzymology of Hallucinogens' was written, we have given 1 g doses, dissolved in water or placed in ordinary
capsules, to a schizophrenic patient who had responded dramatically to the original NAD; there was no clinical response. Then she was given 1 g per day of the original NAD; once more she responded and remained very much improved for nearly six weeks when, there being no more NAD, she quickly relapsed and is still ill.

"This difference may explain the findings of Kline and co-workers who found no response in 10 chronic schizophrenics. They used NAD placed in simple enteric capsules; in addition, it was 70 percent pure and produced vasodilation (flush) in several cases, indicating that free nicotinic acid was present. However, on the HOD test, completed by eight of their total group of 20 (four on placebo, four on NAD), there was no change in scores with placebo, but the HOD scores decreased as follows:

<table>
<thead>
<tr>
<th>Paranoid scores</th>
<th>575 to 325</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception scores</td>
<td>14 to 1.75</td>
</tr>
<tr>
<td>Total scores</td>
<td>63 to 40</td>
</tr>
</tbody>
</table>

"It is not possible, therefore, to determine whether their lack of clinical response was due to a form of NAD that did not survive passage in the gut, or whether they used too little, or whether it was due to the chronicity of their subjects. All of our series of 17 were chronic, but only one had been severely injured by many years of continuous hospital treatment.

The committee apparently did not read this addendum.

Finally, the committee finds it interesting no additional studies have been reported. This is due to the fact we have been unable to obtain any more NAD. The Kline report effectively killed any interest that drug companies might have had and none have been willing to invest large sums of money in any further studies. If and when we obtain more supplies we will be the first to renew our studies. We found it less interesting and more annoying.

However, whether or not NAD is finally established as a therapeutic agent is of little relevance to the pragmatic question, does vitamin 133 work. It is of immense theoretical significance, but not of practical value in the megavitamin B3 debate NAD is not nicotinic acid or nicotinamicle even though many psychiatrists are not aware they are different.

The Diagnosis of Schizophrenia

It is not unusual for psychiatrists to play the diagnostic game if this will save their own hypothesis. This is a problem we have encountered since we began our research. In 1953 one of the patients admitted into our double-blind controlled experiment was screened in the usual way. His psychiatrist diagnosed him to be paranoid schizophrenic and this was in agreement with the clinical director. AH as Director of Research also concurred. After two weeks on medication he was nearly well whereupon his psychiatrist maintained that since schizophrenics cannot recover so quickly he was not schizophrenic. As a result he did not follow medication at home and soon relapsed to be admitted in an acutely paranoid psychotic state requiring a series of ECT plus nicotinic acid. On decoding we found he had been on nicotinic acid. He remained well for 13 years with no medication, relapsed and required two further admissions after a near-fatal suicide attempt. On vitamin 133 he recovered in 1966 and has remained well ever since. Time subsequently removed all doubt about diagnosis.

Recently a recovered schizophrenic on vitamin therapy applied to an eastern Ivy League medical school. He honestly described his illness and recovery fully expecting he would not be accepted. To his surprise he was. The admitting committee told him that since schizophrenics never recover he could not have been schizophrenic. This is the game—if you recover you obviously have not been schizophrenic. This is the game—if you recover you obviously have not been schizophrenic. The committee plays this game well. Wittenborn had such a careful screening system that a few patients believed to be schizophrenic were later rejected. Later from this
purified group he found 24 who as a group did respond well (half on placebo got worse on tranquilizers), but since they did do well he assumes they could not be schizophrenic, following the committee rule, "if you recover you are not schizophrenic." 

At the bottom of Page 24 the committee repeats its false assertion that CMHA studies were negative. We will not repeat the counter claims which have already been discussed.

The second paragraph of Page 25 is a totally misleading account of our work. This would have been obvious to anyone who has consistently and accurately read our reports. Our criteria for diagnosis have consistently remained that used by most psychiatrists. The HOD test was always an adjunct, never primary. We have not run any more double blinds because having directed four of them there comes a point where further repetition is wasteful of time and money and does not convince. One properly run double blind which truly reproduced our original double blinds by Ban and Lehmann would have been more valuable than a dozen double blinds run by us. We have never depended upon either HOD or mauve factor for any of our double-blind experiments. In fact, our first two were completed before the mauve factor was discovered and the HOD test developed.

The committee then devotes Pages 25 to 35 to discussing the HOD which is gratifying as it may arouse interest in our test (as it has already done), but is a complete waste of space since we did not do HOD testing in any of our double-blind experiments.

There are, however, a number of false assertions about the HOD test such as the statement it has never been studied for validity and reliability. Each test kit contains a manual which carefully describes these aspects of the test. Over 3,000 test kits have been sold, but apparently not to any member of the committee. Had they inquired from us we would have advised them of the presence of this data. They referred to one negative report by Stewart and Mahood (1963), but did not bother to refer to a subsequent paper when thei; errors and inconsistencies of this paper were discussed (Kelm et al., 1965).

As with so much of the committee's report there was a rigorous avoidance of a searching analysis of all the HOD reports. The fact that they were able to find only one negative report compared to over one dozen positive reports indicates that there has been a rather widespread use of this simple test.

The mauve factor work is reported in an equally biased way. In our first papers we reported that the presence of mauve factor cut across all diagnostic groups, but the committee tries to leave the impression we claimed it as a diagnostic test invariably related to schizophrenia. Thus, it is not surprising that "other workers (90) (O'Reilly et al.) found the mauve factor to appear across diagnostic classes." O'Reilly was our colleague and under our direction set up the laboratory to run mauve factor assays at his hospital.

The committee's basic premise seems to be that none of the orthomolecular research is of any value. Therefore, they grasp at any research, no matter how badly done, which supports their "preconceived conclusions", no matter how wild which supports them. This they have done with their brief examination of the mauve factor research. They ignored all the work reported from Dr. Carl Pfeiffer's laboratory relating mauve factor (kryptopyrrole) to loss of pyridoxine and zinc.

None of the early workers with mauve factor had suggested that it was an endogenous hallucinogen because it had not been tested. The committee anticipated such a conclusion and on a priori grounds concluded it was quite unlikely. It had this kind of activity they also, based on the committee's propensity to seize upon observations to bolster their own, preconceived conclusions. Recently, Walker (1975) concluded that "kryptopyrrole decreased EEG voltage, disrupted synchronization and induced abnormal;
spiking at a variety of cortical and subcortical sites. Intermittent periods and low frequency hypersynchronous EEG activity were consistently elicited by kryptopyrrole. These waves bear a resemblance to the hypersynchronous EEG pattern associated with hallucinatory agents such as LSD-25. Marked behavioral alterations were observed following the initial injection including ataxia, hyperventilation, locomotor depression, and catalepsy. Kryptopyrrole causes major central nervous system dysfunction and these findings are discussed in the context of a drug-induced model of psychoses.

In his final paragraph, Walker concluded, "Hoffer and Osmond have proposed that mauve factor now believed to be kryptopyrrole represents a metabolic anomaly that is associated in an etiological fashion with certain psychiatric conditions, particularly schizophrenia. They maintain that the disappearance of this biochemical anomaly is statistically associated with psychiatric improvement. The results of the present study strengthen the Hoffer-Osmond hypothesis by demonstrating that the introduction of kryptopyrrole into the mammalian body is behaviorally and electrophysiologically disruptive. The abnormal behavioral reactions and EEG patterns associated with kryptopyrrole provided evidence that this compound has a serious detrimental effect on normal brain function."

This report by Walker effectively demolishes the committee's speculation that kryptopyrrole could not be an endogenous hallucinogen. It has, so far, not been tested on humans, but in view of Walker's report, we doubt whether members of the committee will be rushing out to try it out on themselves. We trust that after digesting our objections to the methionine study they will not be tempted to use it on unsuspecting patients.

This statement on Page 35 is a typical committee falsehood: "Although the evidence suggests that both 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." Each reader will have to determine the accuracy of these conflicting views by reading the literature. There is no substitute for reading the literature oneself.

On Page 36 there is another typical misstatement. Before modified ECT came into general use, we did use ECT as did everyone else, unmodified, but when it came into general use, it became part of the entire orthomolecular program.

Quantitative Aspects

The arguments in the last paragraph on Page 40 and in the first paragraph on Page 41 have been effectively answered by Pauling (1974).

Their discussion on toxicity is bizarre to say the least. If the committee had found real evidence for toxicity, they would have shouted it to high heaven. Had they treated the toxicity of any commonly used tranquilizer in the same way, they would be ethically bound to try and force it off the market. Hoffer has adequately replied to their biased reporting. It is important to remember that as codiscoverers in 1954 of the hypolipidemic properties of nicotinic acid, we have had more experience than any other physician with the potential side effects and toxic reactions. The first reviews of these aspects were ours, appearing long before any member of the committee was even aware of our vitamin B3 work (see Hoffer, 1962).

Conclusions

Our criticism of the committee and their report is that: (1) The committee was in composition biased, failing to contain anyone who was familiar by personal experience with orthomolecular therapy. Not only was the composition incompatible with fairness, it could not possibly even seem to be fair. (2) The procedure used by the committee failed to insure any objectivity or fairness for: (i) they did not obtain any evidence from anyone using orthomolecular therapy;
(ii) they selectively examined the literature using the rule that any double-blind study or allegedly double-blind study (even if it were not like the Wittenborn and Ban studies) was evidence if it yielded negative results while conversely no clinical study if positive was scientific. The four original double-blind studies from Saskatchewan were suspect since we did them, so were not evidence; (iii) the report is characterized by falsehoods, direct and by inference, by biased statements, by use of brief sentences taken out of context, by omissions which always favored the committee's view; (iv) the report was written in order to bolster the committee's negative conclusion.

Unfortunately, the committee was correct in their assumption that most psychiatrists who read their report would accept it at face value and would not check their references. The report has had a pernicious effect in dampening interest in orthomolecular psychiatry. While this will not hurt any orthomolecular psychiatrists it will condemn hundreds of thousands of patients to a lifetime of tranquilized chronicity.

Fortunately, the number of orthomolecular physicians is increasing rapidly while the families of schizophrenics become increasingly knowledgeable about the illness and critical of the Establishment's posture.

Community psychiatry, which is essentially an expensive system for delivering tranquilizers to chronic patients in various shelters, is coming more and more into disfavor. Psychiatrists are sinking lower and lower in both public esteem and in the esteem of their nonpsychiatric medical colleagues. The printing and distribution by APA of a report so bigoted and biased as the Task Force Report can serve only to drive the psychiatric profession lower in public esteem.

In a recent editorial in the Canadian Psychiatric Association journal W T B. (1975) after summarizing the pros and cons of orthomolecular therapy concluded: (1) Nicotinic acid or nicotinamide when used as an adjunct to conventional therapies such as barbiturates and ECT as reported earlier by Hoffer may have a beneficial effect in the treatment of some patients suffering from acute early schizophrenia. As far as is known, no attempt has been made to duplicate these earlier studies (2) Megavitamin therapy has not been demonstrated to be generally efficacious in the treatment of the vast majority of chronic schizophrenic patients.

He concludes, "Orthomolecular psychiatrists should be invited to return to the forum of conventional psychiatry in order that they might be given audience. Their articles should be submitted to conventional journals and should be received with the same enthusiasm and cordiality as other submissions, provided the general criteria of the journal are met."

This is the first comment in any psychiatric journal where an attempt is made to be fair. The editorial writer is not fully aware of the degree of misinformation and bias in the committee's report, but he has achieved adequate awareness to reject the committee's conclusions.

Controversy is part of the history of medicine and is essential to it if medicine is to continue to advance. There will always be an establishment of ideas, some of which will eventually be proven wrong. Thus, there will always be a controversy affecting various parts of medicine. However, worthwhile though it is, there would be a lot less emotional controversy if physicians followed the basic rule of science, i.e., follow the same procedures and conditions when attempting to corroborate. If this rule were rigorously followed it would not, matter whether the scientist was positive or negative about the study but since this rule is seldom followed it does: matter a good deal if the investigator has a negative bias toward the original work he will conduct his studies in such a way as to maximize the negative conclusions and will then discontinue them. There are many examples of this from the reports of hostile anti-orthomolecular
psychiatrists. If they had run their studies more scientifically and longer they would have run the risk of seeing positive conclusions. A scientist with a positive bias may make the same error. But in general the error of the negatively biased psychiatrist is much more serious. In our opinion the failure to use a treatment which is beneficial is much more serious to patients than the error of concluding that a nonactive drug is active. For in the latter case it will soon be shown that the treatment is ineffective, especially if it has to compete with other more useful treatments. Destroying a useful treatment by sloppy hostile research may prevent its reintroduction for several decades. This would insure that large numbers of patients will have lost their chance and will be condemned to a lifetime of unnecessary ill health.

Moss recently (1975) was severely critical of the UGDP studies on tolbutamide. The results from these double-blind controlled studies indicated that tolbutamide was more hazardous than placebo for diabetic patients. But Moss is in total disagreement with this conclusion. Writing, "No amount of statistical manipulation can compensate for the erroneous conclusions that are drawn from a study in which one-quarter did not have the disease, three-quarters should not have been given the drug, the wrong dose was used and the treated group had twice as much pre-existing cardiovascular diseases." "The value of any therapeutic agent should be judged by the benefits that are obtained when it is used properly and not by the harm that results when it is used indiscriminately."

Moss pointed out that 23.8 percent of the treated sample did not have diabetes according to standard criteria, 54 percent had fasting glucose levels under 130 mg percent and did not require tolbutamide, 50 percent were more than 33 percent overweight and should have been treated by a lower calorie diet. Only 27 percent of the entire group were proper candidates for tolbutamide treatment. The dose was constant whereas it is generally accepted it should be increased with time, and base line cardiac risk factors were twice as high in the treated group. Twenty-five percent of the treated group had abnormal ECG while only 4 percent of the control group showed similar abnormalities.

To dramatize his objections Dr. Moss posed a number of questions:
1. How can one evaluate treatment in patients who do not have the disease?
2. How can one evaluate a drug if only 46 percent of the group have hyperglycemia?
3. How can one evaluate a drug if one-half should not have been given it?
4. How can one evaluate a drug when the wrong doses are given?

Our objections to the negative therapeutic trials upon which the committee leaned so heavily are the same. How can one evaluate the benefits of a drug (or of a treatment program) when only a small proportion of the groups used were of the kind that could respond, when the treatment program was not followed, and when idiosyncratic criteria for improvement were used such as milligrams of tranquilizers required and number of days in hospital during which treatment was started.

Another controversy, this time involving the drug propranol, aroused Dr. Lasagna to write, "Some (speaking of the FDA advisory committee) appear to have gotten hung up on the concept of the totally satisfactory paper! The only totally satisfactory papers are fraudulent. Every experiment has deficiencies and the problem is to decide whether the deficiencies are so great as to render the experiment totally useless."

The committee has demanded that our experiments must be totally satisfactory, but have for obvious reasons not followed the same impossible rule for their own favorite papers.

They are unaware of Dr. Samuel Johnson's rule, "nothing will ever be attempted if all possible objections must first be overcome." They demand of us that our first double-blind experiments started in 1953 should have anticipated all the newer findings and complications discovered many years later.
The last controversy concerns DMSO, recently discussed at the third DMSO conference, New York Academy of Sciences, 1974 (see annals New York Academy of Sciences, 1975). On the basis of flimsy evidence the FDA literally banned the use of DMSO. Arthur L. Scherbel in his summary of the conference stated, "This new policy resulted in the abrupt discontinuation of clinical investigations of DMSO because of the appearance of lens changes in certain animals that were receiving high doses of DMSO. This decision was made despite the fact that no eye changes had been reported in humans receiving DMSO.

Among the suggestions he made were "a consulting committee should be appointed by the Food and Drug Administration to evaluate future scientific data pertaining to DMSO. At least 50 percent of the members of this committee should have personal scientific knowledge of DMSO and experience in using it."

Like nicotinic acid, DMSO cannot be double blinded. Thus Kantor (same volume) wrote, "as has been pointed out on many occasions, certain biological characteristics of dimethyl sulfoxide almost precluded a double-blind study of its therapeutic effectiveness in man. Almost without exception when it is applied in concentrations above 10 percent to the human skin, there is a burning, stinging sensation and after percutaneous absorption, a metabolism to various sulfides. These latter appear on the breath; they have a distinctive garlicky odor. True double-blind studies may be impossible."

It is our hope that a critical reader who has followed this narrative and perused the appendices will now be in a position to ask himself those very questions which it was the duty of the APA Task Force to have addressed themselves to, about five years ago.

The data represented here is of several kinds and requires thoughtful consideration.

First of all there are the original double-blind studies undertaken in Saskatchewan of which there are four different series: (1) the original study done at Munroe Wing, (2) a group of studies undertaken at the University Hospital, (3) Dr. O'Reilly's study done at the mental hospital at North Battleford, (4) Dr. Denson's study at North Battleford. In addition to this, there is a great deal of clinical data from clinicians who have used our approach for several tens of thousands of patients. This data is no less important than the double-blind studies on the grounds of sheer volume alone. The belief that double-blind studies alone are valuable is held by the naive, whose knowledge of scientific history and methodology is usually limited and sometimes nonexistent. As we have shown, many authorities doubt whether the double-blind studies yield the kind of information required and some believe that they are unethical. As we shall see, this ethical impropriety has played an important part in the work of some of our critics who have tried to reproduce our studies.

It seems unlikely that there are any sure-fire scientific methodologies which when properly done are error proof: double-blind studies undoubtedly have a place, but are not a substitute for clinical studies and as a number of authorities have emphasized, clinical studies have precedence over double-blind studies. As we pointed out many years ago, double-blind studies, by depriving the patients of information, greatly reduce their interest in and tolerance of a new treatment, thus encouraging errors of the second sort (Hoffer and Osmond, 1961, 1963).

It would seem unwise to begin double-blind studies before one has become thoroughly acquainted with the use of the treatment one is studying. Indeed, it is probably not merely unwise but unethical, because one would know nothing about the possible complications. In retrospect it appears that ours' initial work in Saskatchewan may have been an error in this direction. However, since then we continued to do normal clinical studies while at the same time under-taking the double-blind ones, we avoided errors that seemed to have been committed both by Ban and Lehmann at McGill and by Wittenborn and his
Patients are unlikely to participate freely and willingly in the experiments unless they believe that those who are doing them have some faith in what they are doing. Such faith can only be obtained by learning to use a particular instrument and finding out whether it works or not. It seems likely that if something does not work for a particular investigator in clinical studies he would be well advised not to pursue the matter any further. Dr DeLiz (1973) reports that in the Marlboro study the negative bias against the use of niacin was so obvious that patients took matters into their own hands and went out to get the vitamin for themselves. When we first heard of this we thought it was an unprecedented event, but Dr Shapiro’s (Blumenthal et al., 1974) recent findings suggest that perhaps few double-blind studies escape this pitfall. Patients do not like being hoodwinked about serious matters. Revelations about the ways of experimenters over the last decade or so have seeped through to patients so that we have heard them say, “then they slipped me a placebo.” Science doctors in their zeal to obtain a sure-fire method of eliminating bias have simply produced other biases which may be of an even more serious kind.

In the New Jersey studies, for instance, the loss of patient cooperation and trust resulted in patients deliberately breaking the double blind. Apparently this was not seen as very serious because the experimenters themselves had already broken the double blind due to a peculiar skin condition which seems almost idiosyncratic to New Jersey. In the New Jersey studies, then, we know that in at least nine cases the double blind was broken, more than 10 percent of the sample. Nevertheless, the APA continues to refer to this study as a double-blind study and to puff it with this favorable adjective. It is nothing of the kind. Double-blind studies are like Caesar’s wife, if they are to maintain their reputation they must be above suspicion. Arthur Shapiro’s work suggests that none are above suspicion, but the New Jersey study was not merely suspicious, but unequivocally broken, according to those who participated in it. There were many other objections, too, not the least being the small dosage of niacin used, the chronicity of the patients, and the biased sample—those on niacin had been ill patients 50 percent longer, 58 months as against 36 months. Nevertheless, in spite of this, there is evidence that at least a third of the patients benefited in a differential way, showing that for them, niacin had valuable properties. In order to explain this unwelcome development the Task Force members had the gall to suggest that these patients were not truly “schizophrenic.” This gives the game away. If you benefit with niacin, then you are not truly schizophrenic. This is the kind of science which the Task Force recommends to the public. This is as helpful as Kraepelin’s view that only those who deteriorated completely were truly schizophrenic. According to those who did the New Jersey study, about one-third of the patients studied were not schizophrenic because they responded well to niacin. The question must be asked, how then do we know that any of the New Jersey patients were schizophrenic?

The New Jersey study, then, was one of those half million dollar flops with which NIMH has, from time to time, distressed even its loyalist supporters. Whether this should be ascribed to bias or incompetence depends upon the evaluator’s bias. Was it worth so huge a sum of money? Indeed, one of us with a colleague whose reputation as a psychopharmacologist is widely admired had been prepared to do a similar study for a modest eight thousand dollars some years before.

While the New Jersey studies are unusually expensive those north of the border in Montreal, undertaken by Doctors Lehmann and Ban, were on a more modest scale, but once again exhibit certain curious features. There is no evidence that Dr Ban, who seems to have been most responsible for these clinical testings, ever attempted to learn
how to use megavitamins in the accepted way by the late 1960s when he began his experiments. As we have noted, Dr Ban's experiments are criticizable on many different levels. It was objectionable and improper that he was allowed to double up as a critic and an experimenter and that he failed to meet undertakings such as his pledge not to discuss these matters until his experiments had been completed. Such actions throw some doubt upon his good faith and make it necessary to scrutinize his work very carefully. Since this work has been endorsed by the American Psychiatric Association, the Canadian Psychiatric Association, and the Canadian Mental Health Association, their good faith and judgment must be measured by what they have endorsed. We have shown that there are many technical objections. The evidence is that in one experiment at least, the experimenters acted with a disregard for the well-being of their patients or subjects. It is staggering to think that in the 1970s two reputable medical associations would stake their reputations on an experimenter whose actions in any other context one hopes they would have condemned.

However, before paying attention to this abominable experiment and the implication which is attached to it, it is important to recognize that few, if any, of the Ban-Lehmann experiments appear to have been double blind. In the New Jersey experiments, these studies were supposedly double blind, but as we have noted, great doubt can be thrown upon their authenticity since both Dr. Wittenborn and Dr. DeLiz say that one way or another a substantial proportion of those taking niacin were decoded before the ending of the experiment. Although it now appears that very few double-blind studies are double blind, there is no excuse for misleading the public, particularly when self-praising remarks about 'well-controlled double-blind experiments' are made by those who should know that these experiments cannot be described in this way. In most circumstances, conduct of this kind is referred to as lying. White lies perhaps in a good cause, but lies all the same. Those who claim to be undertaking confirmatory studies in matters which affect the well-being of thousands of patients must not be surprised if even such minor deceits as these are brought to the public's attention. Public money has been spent on these matters, and the public has a right to know how well its supposed guardians have been acting. If the guardians acted dubiously over the double-blind studies and if, as Professor Pauling has pointed out, some of the conclusions are sufficiently skewed as to make one suppose that bias was involved, then the public must judge for itself.

But at least one experiment to which the American Psychiatric Association, the Canadian Psychiatric Association, and the Canadian Mental Health Association have given their approval is unethical and incompetent. In this experiment, Dr. Ban states that he withdrew chlorpromazine from a group of schizophrenic patients who had been on it for some time. These patients were then given 3 g of niacin per head. Another group of patients had the chlorpromazine withdrawn and were given a placebo. Those on the placebo got worse as one might expect, but those given the niacin not only did not get worse, the evidence suggests they became rather better. This is a most encouraging finding, particularly today, when we need to be able to reduce the long-term use of chlorpromazine and similar phenothiazines as much as possible because of tardive dyskinesias and other damaging neurological conditions, which occur most often in those who have been on these substances a long time. So far, there is nothing wrong with this experiment; indeed it shows that niacin had some unexpected uses for chronic patients. An alert and intelligent clinical experimenter would have pursued this lead.

It was at this point that Doctors Bang and Lehmann introduced a new element, which was both scientifically absurd and ethically dubious. Those who had been
removed from chlorpromazine and were being well supported and even improved by niacin were then given 20 g of methionine per head. Not unexpectedly they became very unwell. Dr Ban and Dr Lehmann stated that this showed that niacin did not prevent transmethylation effects of methionine. When Dr Lehmann was asked about this by Professor Pauling, at an NIMH meeting, he apparently did not realize how inept he and his colleagues had been. Three grams of niacin could not possibly be expected to counteract the effects of 20 g of methionine in addition to preventing the recurrence of symptoms after stopping chlorpromazine. At best one can say that to plunge patients, who had been improving somewhat on niacin, back into madness, which could not possibly help them, and from Doctors Ban and Lehmann’s account, gravely harmed them, is the kind of unethical experiment which since the Nuremberg Doctors Trials has been universally condemned.

If the American Psychiatric Association, the Canadian Psychiatric Association, and the Canadian Mental Health Association are so indiscriminating in the kind of experiments which they support and which they use to discredit orthomolecular psychiatry, then surely we can hardly be surprised that psychiatry itself is, according to its leaders, in a state of confusion.

Confusion is often thought to be one of intellectual confusion, due to model muddles. But in this case, moral and ethical confusion has been demonstrated, and it is that moral and ethical confusion which has fuelled much of the attack on megavitamins and has resulted in otherwise competent people undertaking experiments in a curious way which they would condemn in their own pupils, and would attack most vigorously orthomolecular psychiatrists been equally slack and heartless.

In recent years political and scientific establishments have acted as if they believed that they were above the law and above scrutiny. As regards politics, this is now becoming unacceptable and we must hope that the same will apply to medical and scientific establishments. Psychiatry, with its knowledge of in-built human biases, ought to be particularly sensitive in this respect; unfortunately, as this report shows, there is no evidence that our colleagues have succeeded in avoiding those biases which they would be the first to condemn in others.

It appears to us that the current uncertainties and misfortunes in psychiatry have been amply documented by its leaders, including Dr John Spiegel, APA President in 1975. We believe that these uncertainties resulted in a vigorous and indeed vicious attack on orthomolecular psychiatry. This, no doubt, serves to work off the anxiety and hostility generated by current frustrations faced by the psychiatric establishment. It is like kicking the cat or bawling at the children because one feels upset and bad tempered. There is no reason to dignify it with any of those fine long words which make it sound more respectable. This is a technique that Hitler employed regularly, and it explains such behavior but it does not excuse it. Publicly recognized associations of professional people have a duty to examine and correct their own biases. Failure to do so is especially reprehensible among psychiatrists because they claim that this is one of the useful functions they perform for society. The public may very well ask, who will guard the guardians?

Their Goal

We had President Busse’s personal assurance that the Task Force as well as the Council was composed of highly qualified psychiatrists who were familiar with the scientific method and were capable of evaluating published literature. The reader will judge whether Dr 13usse’s evaluation and expectations were correct. We agree that the Task Force could have accomplished this task, but they did not do so. Perhaps one day the professionals involved in this debate will ask themselves why this particular kind of mistake was made and how it can be avoided in future.

The bias of three members of the committee was so open that one of us,
AH, objected vigorously at the beginning of the survey. The first evidence of this was Dr. Morris Lipton’s lecture in California at a public meeting where he openly stated his strong opposition and bias against the orthomolecular approach. He also demanded that the chairman, Dr. Ross MacLean, provide him with more time than was allotted to him or to anyone else, because he was the only critic of orthomolecular psychiatry.

Since three of the five Task Force members made no attempt to hide their bias against orthomolecular psychiatry, this raises serious questions about the conduct of the American Psychiatric Association itself. How could a professional and scientific body allow an inquiry, conducted under its aegis, to be undertaken in a manner which in any other circumstances it would have certainly condemned? Would the APA countenance an investigation of psychoanalysis or community psychiatry using a task force the majority of whose members were openly prejudiced against these activities? Would the APA attach any importance to the findings of such a committee, and would anybody be surprised if psychoanalysts and community psychiatrists were unwilling to accept such a report?

Why then did this Task Force and those who appointed it behave in a way which was clearly open to criticism and even censure? It would be poor taste to subject our colleagues on the Task Force to that personal psychodynamic scrutiny which Senator Goldwater received about a decade ago from some hundreds of APA members. However peculiar these activities may appear when set out in print, we do not ascribe them either to personal psychopathology or to bad faith. There is no need to when three committee members have never denied their bias.

Lipton did not reply to a letter accusing him of being prejudiced and requesting that he remove himself from his position of Chairman. Mosher was quite explicit about his point of view. The reader can judge for himself whether his is the stance of an unbiased man. Why then did the American Psychiatric Association show such faith in the lack of prejudice of those who had not concealed their prejudice?

Where important matters are concerned even the faintest suspicion of bias is usually sufficient to disqualify those charged with fair judgment. We infer from the absence of these customary safeguards that the main objective of the Task Force was to defend the establishment against our disturbing opinions. A second and more respectable objective was to protect the public against false hopes and mistaken expectations, for many members of the establishment had become convinced from their deep knowledge of psychiatry that the orthomolecular claims must be without merit:

Any group with such good ends in mind might behave much as the APA did, but, however praiseworthy their intentions, actions of this kind have been a frequent source of error in medicine. These good intentions made the means to be used of lesser importance, so that the APA establishment became unable to adopt a judicial stance other than that of judge Lynch.

However honorable the goal the mean employed negated all favorable reports found in the orthomolecular literature: and led the Task Force to ignore any supporting evidence even when it derived, as with Wittenborn, from experiments approved by the committee. How could this happen? In our opinion the most economic explanation lies in the atmosphere and ambiance of Washington during the early 1970s.

It is now evident that at few times in the history of the United States have those in authority believed more sincerely that this gave them license to use any means to further ends self-evidently good. Bad habits in big governments spread to little governments. The American Psychiatric Association is the "little government" of psychiatry in the U.S.A. In this matter the APA had the support and cooperation of the National Institute of Mental Health, (1) a huge bureaucratic organ of big government.
which has never disguised its dislike of orthomolecular psychiatry

Perhaps psychiatrists should ask themselves just how and why, in spite of their study of the mind and heart, they too were seduced into a ruthless urge to employ massive authority against minority opinion. By yielding to this temptation the American Psychiatric Association became contaminated with that spirit of intolerance which was abroad in Washington at the time. It is now often called 'Watergate.'

Appendix

We have made a large number of serious charges against the Task Force Report published by the American Psychiatric Association. Our main charge is that the committee had already arrived at their negative conclusions long before they examined the literature available to them and that they tailored the report in order to bolster their biased conclusions. As science students we used to talk about how some students cooked the data, i.e., manufactured the data necessary to support the conclusion they knew they would have to reach. This the committee did by a selective examination of the literature, by avoiding references to most of the collaborative reports, by downplaying or ignoring any positive data in what they considered reports favorable to their own point of view, and by so distorting and misinterpreting data in our original work as to turn our positive conclusions based upon our observations into their negative conclusions. These they based upon tactics such as ripping statements out of context, reporting from tables in a misleading way, and generally conducting themselves in such a way that no matter how hard anyone familiar with the literature might try it would be impossible to have even the appearance of scientific objectivity. Scientific dishonesty is a serious matter, especially in this case, to the hundreds of thousands of patients who will be deprived of a chance to recover with orthomolecular therapy.

The question of honesty in science has been discussed frequently in Science, a publication of the American Association for the Advancement of Science, and in the public press. Thus, Robert C. Cowen in the Christian Science Monitor for March 26, 1975, opened his report on "Corruption in Science" with the following paragraph:

"Fear, fame and fortune seem to be replacing the challenge of the unknown as the driving force of much that passes for scientific research."

There are two main types of corruption in science reporting. Scientists may report data in such a way that it cannot possibly be reproduced no matter how much one would wish to do so, or in very rare cases the data may have been entirely fabricated. And in the second way, the literature review around which the report is built may be presented in a manner calculated, not to provide a fair view of what has been done, but to prove a conclusion gained by other means. Cowen's strictures against corruption in science are supported by Marc Lappe in his report to Science. Thus, Lappe wrote, "Those who practice it know that the nature of the scientific enterprise itself hinges on the scrupulous integrity of its practitioners."

In a memo to Hoffer dated March 27, 1975, Osmond wrote:

"Sometime ago I suggested in a memo that it was not fanciful to suspect that the ethics which we saw at work during the Watergate affair had not been confined to politics. My particular concern was with the behavior of the APA Task Force and with its Canadian counterpart of Ban and Lehmann. We know from our own experience in Washington that high federal officials have countenanced dubious behavior as regards our work. We also know that the APA used its house organ Psychiatric News to attack our findings while refusing or being very tardy about publishing our rebuttals. We also know from very unpleasant personal experiences that the APA ethics cam-

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Two of the members of the Task Force were working for the National Institute of Mental Health.
committee was used to attempt to dissuade us from discussing the megavitamin work publicly. In the encounter that AH and I had with that committee in the fall of 1970, it was evident that its members did not know very much about our many published papers. They seemed to believe that we had reported first to the public, a habit only too frequent today which, however, we did not do on principle. Reporting first to the public is the scientific equivalent of the political leak and is used to steal a march on opponents. It seems to have occurred in the notorious Sloan-Kettering affair.

"It is unlikely that so important an activity as science can be apolitical: apart from anything else its political consequences are so vast, but just because politics impinge upon it so heavily, that it is the duty of scientists to insure that its morals and ethics are not eroded. The politicians among scientists have always been there and some of them have been magnificent scientists. Isaac Newton was a Member of Parliament. Benjamin Franklin was a marvelously adroit diplomat, while Benjamin Thompson, Count Rumford, was an extraordinary combination of soldier, spy, traitor, gunmaker, and pure physicist. The important thing is that although Newton and Rumford were difficult and cantankerous men they were not cheats and they were devoted to science. They strove to enlarge truth. There is much evidence that the APA Task Force, far from wanting truth enlarged, much preferred that it be suppressed."

"Of the one-third of the patients who benefited significantly from niacin in the Marlboro Study it seems a little bizarre to suggest that they were not really schizophrenic. This suggests that those who respond positively to niacin are thereby not schizophrenic. However, if the NIMH study misdiagnosed one-third of their cases, why not the other two-thirds? Ban's use of large doses of methionine comes in a similar category but worse since it actively harmed people who were improving on niacin. If a man's judgment is so unsound in one direction can you be sure of it in another?"

"The failure to report the breaking of the double blind at Marlboro was another error suggesting bias to even the most well-disposed. Not being among the best disposed to the APA-NIMH junta I am inclined to take these signs at their face value. It would be a little improper in psychiatry not to give one's adversaries the full benefit and courtesy of psychodynamic interpretations."

The grand strategy of the committee was to provide as much support as possible for the conclusions they had already arrived at before they began their studies, namely, that orthomolecular psychiatry had no merit as a treatment and at its worst was a fraud. Once that strategy had been conceived the tactics used followed logically, being based upon the philosophy of the ends justifying the means. Their ends were to protect the public from the evils, errors, and dangers they knew were inherent in orthomolecular psychiatry. Therefore, any method, no matter how objectionable it might be in another context, would be permissible, even desirable.

Inherent in these tactics was then the assumption that they could get away with it since very few members of the American Psychiatric Association would read the original reports with care and diligence. The committee naturally assumed that their own status and prestige as members of an APA subcommittee of a research committee would satisfy the members of the APA. Unfortunately, they were correct.

Several years ago at a press conference in New York City, arranged by the American Schizophrenia Association, Drat Linus Pauling was questioned about his views on ascorbic acid and the common cold. He was asked by a well-known science reporter, known for his advocacy of establishment medical views, why if ascorbic acid was so good in preventing colds, was it uniformly rejected by most physicians? Dr Pauling opened his reply by stating, "I think I am the only person who has read my book." He then
analyzed his conclusions that there was adequate evidence in the medical literature to warrant research relating ascorbic acid to the cold and that he had made an attempt to draw this to the attention of medicine to encourage them to proceed with these studies. We have often felt that we and other physicians practicing orthomolecular psychiatry must be the only ones who have read the orthomolecular literature.

Our charges against the committee’s report are based upon what was written in the literature and how it was reviewed by the committee. So that each reader can follow our argument in detail and check our conclusions we are attaching an appendix. It contains the following information:

1. A brief abstract of all the reports which we have authored which deal with aspects of orthomolecular psychiatry. We also make a few comments with respect to the committee’s use of this information.
2. A brief abstract of all the corroborative reports mostly ignored by the committee.
6. Comments on Double-Blind (Placebo) Methodology.
7. Efficacy and Toxicity.
8. Copies of letters to the American Psychiatric Association re Dr. M Lipton’s chairmanship of Task Force Report.
10. Reading list in Orthomolecular Psychiatry.
11. Real attempts to corroborate with failure to confirm original studies.
SECTION I— Brief Abstract of Orthomolecular Treatment by Saskatchewan Group


This was the first major report. We reported that a pilot study to determine dosage, duration of treatment necessary, side effects, and so on was positive and led to the double-blind controlled experiment on 30 schizophrenic patients. This was the second double-blind experiment ever conducted in psychiatry. We did the first on a yeast nucleotide preparation a year before. The groups receiving vitamin B3 (some of whom received ECT) fared much better than the placebo group (an equal proportion receiving ECT). At the end of one year three out of nine placebo patients were well compared to eight out of 10 on nicotinic acid and nine out of 11 on nicotinamide. That is, a one-year recovery rate of three out of nine on placebo compared to 17 out of 21 on vitamin B3. Follow-up evaluations were conducted by a trained worker who was not aware of the treatment code.

We were aware that it is impossible to run double-blind experiments with nicotinic acid for the following reasons:

1. It is impossible to prevent or disguise the flush. Even after patients become used to it, they will now and then have a marked flush, especially in the morning, and will even more often have a pink glow. They are aware of these reactions and it is easily seen by any observer.
2. It tastes sour and no allowance can be made for this. For these reasons no claim for the blindness of any experiment using nicotinic acid can be accepted unless there is proof these factors have been allowed for.

We, therefore, concluded, when used in adequate dosages, nicotinic acid and nicotinamide materially contribute to the recovery of schizophrenic patients.


After discussing our hypothesis we wrote, "Nicotinic acid and its amide arti• methyl acceptors which when they are used in large doses may compete with' noradrenaline for methyl groups and so decrease adrenaline output. This was one reason why nicotinic acid was tried for schizophrenia. The results for early schizophrenia are good. About 15 per cent of our schizophrenic patients require daily administration of this vitamin and relapse a few weeks after stopping it. It does not help chronic-
schizophrenics even when such massive doses as 25 g a day are given for three months " The committee did not read this paper.


In referring to our treatment we wrote, "This consisted of massive doses of niacin or its amide ranging from 3 to 25 g daily " Table 1 from our recent paper outlines our results. These are that while niacin seems beneficial in early schizophrenia and apparently reduces the rate of relapse (one out of 37 vs six out of 36) when medication is continued, it is usually ineffective in long-continued illnesses " The committee did not read this paper.


This was a general review paper comparing results of adding vitamin B3 to standard treatment before tranquilizers came into use ECT was the best treatment then and about half of the patients were so treated.

The results of treating all schizophrenics treated at this ward (Munroe Wing, General Hospital, Regina) between 1952 and 1955 were given as follows:

<table>
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<tr>
<th>Group</th>
<th>N</th>
<th>On ECT</th>
<th>Number sent to Mental Hospital</th>
<th>Number of Suicides</th>
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Thus, out of 73 on niacin 66 were able to remain in the community while out of 98 on other treatment 51 were not readmitted (Chi Sq = P < 0.001)

We also showed the cumulative re-admissions as follows:

<table>
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<tr>
<th>Number of Readmissions</th>
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</tbody>
</table>

Between 1952 and 1955 the readmissions accumulated more quickly in the non-niacin group, but thereafter the relapse rate was nearly the same. We said, "It seems from this that niacin kept the disease in check; but one can hardly expect such a protective action to continue indefinitely " Most of the original niacin group were not receiving any during follow-up. We also reported that from our second double-blind study on vitamin B3, 34 out of 62 had achieved a five-year cure (55 percent) compared to four out of 20 on other treatment (20 percent). From an earlier study, out of 58 treated with niacin (many of whom also had ECT) 45 (78 percent) were five-year cures compared to 34 out of 90 on other treatment (many of whom had ECT), or 38 percent.

Finally, we compared treatment results on three groups treated by other physicians, none of whom had any enthusiasm for vitamin therapy, and some of whom were actively hostile.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Days in hospital treatment admission</th>
<th>Discharge status well and much Improved</th>
<th>Readmitted</th>
<th>N well on last evaluation in community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other treatment</td>
<td>22</td>
<td>25</td>
<td>1</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>ECT only</td>
<td>26</td>
<td>66</td>
<td>5</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>ECT and Niacin</td>
<td>30</td>
<td>60</td>
<td>7</td>
<td>6</td>
<td>24</td>
</tr>
</tbody>
</table>
On other treatment two out of 22 were well (10 percent), on ECT only 10 out of 26 were well (39 percent), while on the combination of niacin plus ECT 24 out of 30 were well (80 percent) None of the patients were seen by us, but we had access to the hospital and follow-up records

We, therefore, concluded, "In our view it is a useful adjunct in the treatment of schizophrenia both for acute cases and to reduce the chance of relapse; and we hope it will be tested on a fairly large scale with a carefully designed follow-up. For with niacin and its amide, unlike the waters of Jordan, one can always try the Abanas and Pharphars of the drug companies at the same time"


In this paper we discussed the relationship of the presence or absence of a mauve-staining factor in urine to diagnosis, treatment, and prognosis We suggested the term malvaria for any person who excreted this factor Since then it has been identified as kryptopyrrole and can be measured quantitatively We also reported results of a brief experiment on 24 retarded children All were tested and then started on nicotinamide using 1 g per 50 pounds This dose, we now realize, was too low The present recommended starting dose is 3 g per day We assumed that parents who saw no improvement would not wish to continue while those who did note improvement would continue

The parents, of course, did not know the results of the urine test Out of 16 mauve-negative children five remained on vitamins, whereas in the same interval out of eight children who were positive none were discontinued As a class parents of mauve-positive retarded children were happier and more optimistic about the results, Chi Square is 7.5, i.e., P < 0.01, this is due to chance


One of the few abstracts which is correct except the committee got the year of publication wrong, one of many editorial errors They dated it 1963 in the body of the report and 1964 in their references

(7) Treatment of Organic Psychoses with Nicotinic Acid (a single case), A. Hoffer (1965)

A patient with an organic psychosis who had failed to respond to several medications recovered within 24 hours after he was started on nicotinic acid and ascorbic acid The decision to begin this treatment was based on a chemical test which showed he had mauve factor in his urine

In a further report, Hoffer (1970a) reported this subject survived 34 months after his inoperable bronchiogenic cancer was established (diagnosed) The last radiological examination before he died showed no recurrence of the cancer The cause of death at age 76 was probably coronary disease Unfortunately, there was no autopsy The committee ignored the case

(8) Malvaria and the Law, A. Hoffer; (1966b)

One of us (AH) reported that out of 740 subjects tested for mauve factor in their urine, 14 had been charged with a variety of crimes Of the group, 10 had mauve factor in their urine This was a very high proportion being similar to the proportion of schizophrenics who test positive When the mauve-positive subjects were treated with orthomolecular therapy most recovered and no longer were involved in further criminal activity Detailed case histories were given The committee ignored this report

(9) Biochemistry of Nicotinic Acid and Nicotinamide, A. Hoffer (1967b).

Here one of us (AH) presented a biochemical review of vitamin B3 including a discussion of side effects and toxicity There was little evidence it was
hepatotoxic The fallacy of the abnormal liver function tests was discussed. "Nicotinic acid and nicotinamide are remarkably safe compared with the whole field of chemotherapy" was the conclusion still valid today The committee ignored this paper.

(10) The Effect of Nicotinic Acid on the Frequency and Duration of Re-Hospitalization of Schizophrenic Patients: A Controlled Comparison Study, A. Hoffer (1966)

In this paper one of us (AH) compared the results of treatment by other psychiatrists who sometimes used nicotinic acid against the results of their standard treatment on similar patients.

Here were the results:

<table>
<thead>
<tr>
<th>Treatment by all Psychiatrists</th>
<th>N</th>
<th>Readmitted</th>
<th>N Readmissions</th>
<th>Total Days in Hospital</th>
<th>Suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic Acid</td>
<td>128</td>
<td>7.422</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>346</td>
<td>54 491</td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

1. The majority of chronic schizophrenics were not benefited.
2. The majority of acute patients given 133 responded much better to treatment when these vitamins were included than the comparison control group.

(11) Nicotinic Acid Therapy and the Chronic Schizophrenic, P. O'Reilly (1955)

This is an important paper because it has been used by opponents as an attack on our work Dr O'Reilly was then a psychiatrist at the Saskatchewan Hospital in North Battleford and was in charge of research under our direction We encouraged him to do this study and helped him have it published. It was important for it confirmed our observations that chronic patients such as those kept many years in the hospital did not respond. We hoped that publication of this report would protect us thereafter from the recurrent attack on our work based upon chronic patients; obviously it did not since even the committee persists in confusing the reader.

O'Reilly referred to three of the possible mechanisms of action of vitamin B3 including its role as a potential methyl acceptor. He selected "eleven of the most refractory, regressed, deteriorated female patients" who had not responded to any other treatment Tranquilizers had not come into use. Mean duration of stay in hospital was 16 years. They were given 3 g per day for eight weeks. They were carefully examined and rated every week. O'Reilly found that the patients improved significantly over an untreated control group of 43 patients (at 10 percent level) in the following areas:

1. Sleep improved in all patients
2. Appetite increased in all patients
3. Directability was better in six.
4. Initiative alone was better in five
5. Cooperation with routine was better in four
6. Care of personal property was better in three

None of the control group showed any significant improvement.

Three patients generally improved and two histories were given to illustrate this. There was no improvement in delusions, hallucinations, and other schizophrenic features.

O'Reilly concluded, "While this trial does not show nicotinic acid to have any effect on the schizophrenic process per se, it is felt that nicotinic acid should be further investigated in a larger trial series." It is clear that we claimed no success in treating these cases even
though their behavior was significantly better. These are patients similar to those given deteriorated, badly prepared NAD by Kline et al. (1967). The committee does not discuss this paper, but erroneously refers to it among its ECT references.


We described five chronic schizophrenics who had failed to respond to any previous treatment. They were treated with our Phases I, II, and III treatment procedures. At the time this report was compiled three were well or much improved. Today one of them, LR, is still well, one, CS, refused to cooperate with vitamin therapy and is today chronically tranquilized and ill. We have no report on the others.

We also reported the following results of treatment achieved by the research division on all patients treated between March 1, 1960, and March 1, 1961:

<table>
<thead>
<tr>
<th>Phase</th>
<th>N</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>N Much Improved</th>
<th>Nsent to Mental Hospital</th>
<th>NSick at Home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

To mental hospital and their home.

We wrote, "Well means that the patients are as healthy physically and mentally as they were before illness struck them. They are free of complaints and function normally at home and in the community. Of 16 patients treated only with Phase I, a total of 14 are well or much improved. These patients were a better group prognostically than were the other two groups. From Phase II a total of 16 patients are well or much improved. Two went to a mental hospital and one is still there. From Phase III (i.e., Phases I and II failures) three are much improved. Thus 33 of 40 treated have to all intents

(13) Nicotinic Acid: An Adjunct in the Treatment of Schizophrenia, A. Hoffer (1963)

Here AH compared readmission data on all schizophrenic patients treated at University Hospital, Saskatoon, between 1955 and 1962. They were all diagnosed and treated by members of the staff not connected with our research group. All standard treatments were also used including ECT, tranquilizers, and psychotherapy. Results are shown below:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>N Suicides</th>
<th>N Readmitted</th>
<th>N Readmissions</th>
<th>Total Days</th>
<th>In Hospital Mar 31/63</th>
</tr>
</thead>
<tbody>
<tr>
<td>all Vit B3</td>
<td>76</td>
<td>0</td>
<td>21</td>
<td>43</td>
<td>2.453</td>
<td>4</td>
</tr>
<tr>
<td>all others</td>
<td>220</td>
<td>4</td>
<td>122</td>
<td>275</td>
<td>25.341</td>
<td>17</td>
</tr>
</tbody>
</table>
AH concluded, “Although many patients are so sick they will not recover on nicotinic acid alone, the majority of schizophrenic patients who have recovered as a result of treatment with ECT or tranquilizers will remain well if they are maintained on nicotinic acid.

"Since vitamin B3 is not toxic and is easy to administer I suggest that schizophrenic patients (excluding those chronically ill in mental hospitals) are not receiving the best treatment if this vitamin is excluded from the therapeutic regimen." Earlier AH had said, "Chronic schizophrenic patients of the type found in mental hospitals do not respond and there is no point in giving them this treatment."

The committee avoided this important document, important since none of the patients were under our care and at that time only nicotinic acid or nicotinamide was used without any other component of orthomolecular psychiatry.

(14) Nicotinamide in the Treatment of Schizophrenia, R. Denson (1962)

Denson selected from new or first admissions and readmissions only those requiring ECT. Out of 41 cases chosen, 36 were able to complete the study. They represented about one-third of the total admissions.

There were no side effects and the double-blind code remained unbroken. At the end of the year there was no significant difference, but eight months later it was determined that group A had done markedly better than group B. The code was then opened and it was found that the treatment group had been the group doing better.

Denson found the following:

<table>
<thead>
<tr>
<th>Group</th>
<th>Days in Hospital (Mean)</th>
<th>Hospital at 5th and 6th Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinamide</td>
<td>1.064</td>
<td>In 1 Out 16</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.775</td>
<td>In 8 Out 11</td>
</tr>
<tr>
<td>Significance</td>
<td>0.05</td>
<td>p c 0.01</td>
</tr>
</tbody>
</table>

The fifth and sixth months were selected because one could not expect five weeks on nicotinamide to exert its effect forever as Denson put it.

(15) Schizophrenia and Suicide, H. Osmond and A. Hoffer (1967).

In this report we discussed the high frequency of suicide among schizophrenics which was about 25 times more frequent than one would expect in any general population. However, the suicide rate for patients treated with orthomolecular methods was very much less.


This was a study to determine if patients already well or much improved on nicotinic acid would relapse if switched over to xanthine nicotinate. A double-blind cross-over design was used. Our conclusion was that the nicotinic acid derivative was just as effective in maintaining the patients.

As we have been accused of claiming nicotinic acid was absolutely safe, we will quote here one of our sentences, "No medication is free of side effects and nicotinic acid and nicotinamide in megavitamin doses are not exceptional. Most of the side effects are irritating and inconvenient rather than toxic."


A single case is discussed.
(18) Megavitamin B3 Therapy for Schizophrenia, A. Hoffer (1971)

This is a general review article trying to correct the many errors and biases then being promulgated by the CMHA studies. Apparently it had little effect since Ban and Lehmann continue to publish as if they had not read this paper and recently Ban was given an award by the Canadian Psychiatric Association for his brilliant work in disproving our megavitamin claims.

(19) Vitamin B3 Dependent Child, A. Hoffer (1971)

The syndrome of the vitamin B3 dependent child is characterized by:
1. hyperactivity
2. deteriorating performance in school
3. perceptual changes
4. inability to acquire or maintain social relationships

A few cases are given to illustrate the use of the orthomolecular approach.

(20) A Vitamin B3 Dependent Family, A. Hoffer (1971a)

A father and his three children, the youngest from a second wife, were all vitamin B3 dependent and recovered on vitamin B3 therapy.

(21) Orthomolecular Treatment of Schizophrenia, A. Hoffer (1972)

A review of the development of orthomolecular psychiatry.

(22) A Neurological Form of Schizophrenia, A. Hoffer (1973)

A young woman first ill with schizophrenia at age 13 developed what was diagnosed as a progressive degenerative cerebellar syndrome. On nicotinic acid, 3 g per day, she recovered.


A general review article.

(24) Five California Schizophrenics, A. Hoffer (1967a)

This was a clinical report of five California patients who recovered on orthomolecular therapy. They had not responded to any previous treatment. There was nothing unusual about this report except that it set off a chain reaction culminating in our appearance before the committee on Ethics of the American Psychiatric Association in December, 1970. Apparently a psychiatrist who was not willing to identify himself complained before the committee. This is an example of retrospective censorship.

The committee on Ethics have since not communicated with us and apparently did not consider our action in publishing a scientific paper unethical.

(25) Niacin Therapy in Psychiatry, A. Hoffer (1962)

In this monograph, the first ever published dealing with nicotinic acid and mental illness, AH described the results of treatment as then known, giving histories of 64 patients treated so the reader would know the diagnostic and treatment orientation.

This book contained a special section on side effects and toxicity. No reference is made to this by the committee who referred only to the Mosher study, a member of the committee.

(26) How to Live With Schizophrenia, A. Hoffer and H. Osmond, final writing and editing by F. H. Kahan (1966 and 1975)

This is the first book written for patients and their families consumed by schizophrenia. It provided our perceptual theory of schizophrenia first elaborated in some detail by John Conolly about 150 years ago. The first edition treatment section was written in 1965 and represents our treatment view then. Since this book was written for lay people we made certain we were very careful in our recommendations. We stated, "If after this treatment has been completed you do not improve, it is because you have been sick so long that the disease has become chronic and treatment will have to continue for a long period of time, either in hospital or at
As a rule patients who have been sick for many years will not be helped with nicotinic acid alone. But if they can be improved in any way whatever it is better to keep them on this treatment.

We also pointed out the need for control of diet, control of infections, control of smoking, adequate sleep, use of medical psychotherapy and other psychosocial aids such as OT and RT.

The treatment outline in our second edition contains the more comprehensive orthomolecular program. We have been accused by the committee of being shifty because our treatment has improved. Using their definition, every modern psychiatrist is shifty since they no longer use treatment available in 1965. The three phases of treatment are discussed, but provision is made for junk-free and allergy-free diets, other vitamins are discussed, and more attention is given to children. The concept of vitamin B3 dependency is introduced as a cause of schizophrenic syndromes and as a cause of some of the learning and behavioral disorders in children.

This book is not a best seller, but has sold over 20,000 copies and continues to sell well.

We have thousands of letters from grateful parents, spouses, and patients, some of whom wrote that it literally saved their sanity since it gave them an alternative view. They no longer were forced to accept the popular psychiatric view that they, especially parents, had made their relative ill. They were for the first time introduced to the medical model of schizophrenia.

(27) Controlled Study of Orthomolecular Therapy on Children with Learning and Behavioral Disorders (1967-1974)

This was the final report submitted to Mental Health Saskatchewan in 1975. It is the study reported in paper (19). Thirty-seven children under age 14 (with a mean age of 8.3) with a variety of learning and behavioral disorders were treated. They were given nicotinamide, 1-3 g per day, and ascorbic acid at the same dose level. If and when the patient recovered the nicotinamide was replaced by identical appearing placebo tablets. The child was not aware this would be done. The parents were advised about this before they agreed to place the child in the study. If and when the patient relapsed the placebo was discontinued and the nicotinamide resumed. The parents kept records listing when they placed the child back on the active medication. All the children were also placed upon a sugar-free diet. This closely resembles Dr. B. Feingold's diet which excludes synthetic additives to which many of these children react with hyperactivity. Manufactured foods which contain sugar also contain these other undesirable additives.

Of the 37 children who started the program, 21 became normal and 14 were better. At the final evaluation 18 remained normal, five much improved, and the rest were ill or their condition was unknown and they were assumed to be ill. That is, 24 out of 37 are well or much improved. Most of the failures did not follow the program consistently chiefly because the parents could not persuade or force the children to take the medication. The vitamin tablets were rather large for children and capsules were then not available. Only 19 were placed on placebo because some were lost from the study and others had improved so slowly that we did not wish to expose them to the hazards of a relapse. Early in this study it became apparent that many children who relapsed on placebo were set so far back that it took much longer and higher doses of vitamins to return them to good health again. All the patients on placebo relapsed within four weeks, some within two. For example, one child had recovered to the point that he was promoted one grade in school. At the same time he was switched over to placebo. No one at the school was aware of the study, but in a few weeks the teacher called the parents to inform them that they had made a mistake in promoting him and that they were forced.
to revert him to his previous status. When the parents were convinced of his relapse he was placed back on the nicotinamide, recovered, and thereafter had no further problem in class. It was clear that the ascorbic acid did not prevent relapse.
SECTION II—Brief Abstracts of Corroborative Reports

It is important to describe briefly all the corroborative reports. The committee referred to a small number of reports in addition to those we have already discussed (#15, 17, 34, 35, 38, 39); listed a number it could not have seen since they were never published (#33, 36, 37, 40) and they were not present at the meeting.


Dr. Robie was the first psychiatrist to report his corroboration of our work. He described six cases. Since then he has remained an enthusiastic proponent of orthomolecular therapy. Lehmann's first tranquilizer study was conducted on only an equally small number of cases. He also remains an enthusiastic proponent of tranquilizer therapy. Dr. Robie, with over 40 years of experience, observed that on vitamin B3 therapy his patients became his friends. Never before had he experienced this with schizophrenics.


Fifty-nine schizophrenics were treated with orthomolecular methods. One patient was worse, five unchanged, and 43 (88 percent) were improved and much improved. This improvement was assessed by the committee. The same number of patients felt they had been helped. In a later study on tranquilizers, Borda (1973) found that only 21 percent of the patients felt they had been helped compared with 66 percent of their doctors who concluded they had been helped. There is a better consensus for orthomolecular treatment.

Ward confirmed our work that non-schizophrenic patients who scored high on the HOD test also responded well to the therapy. He concluded that "massive dose niacinamide or niacin is of benefit in schizophrenia and in various nonschizophrenic states." As regards neurotics, the committee suggests that all neurotics, not just those who score high on the HOD, do equally well on the orthomolecular megavitamin treatment.


This paper is ignored by the committee.

Four groups were studied:
(a) All outpatient schizophrenics seen at one clinic were given nicotinic acid and ascorbic acid, 3 g per day of each for six months, plus any other medication required.
(b) One-third of the patients from one chronic ward.
(c) A control for group (a) matched for age, sex, diagnosis, duration of illness, and duration of previous hospitalizations.
(d) Control for group (b).

All other patients on the same ward.
These results are statistically significant. On the other hand, groups (b) and (d) did not differ. That is, acute and subacute cases benefited while the mental hospital chronics did not.

(4) Treatment of Schizophrenia Based on the Medical Model, D. R. Hawkins (1968)

The committee ignored this paper. Dr. Hawkins reported treatment results on 315 consecutive patients who applied for treatment at an outpatient clinic. Very strict diagnostic criteria were used. The majority were chronic. Eighty-nine percent had previous treatment. Many had multiple and lengthy periods in hospital of up to 12 years. Almost all had had phenothiazine and other drug treatment often for prolonged periods. Some had over 100 ECT, previous psychotherapy, or psychoanalysis for up to 20 years. A few families had spent $150,000 (by 1968) on ineffectual care.

Hawkins concluded, "The majority of patients improved significantly and progressively. Those in whom the illness began during adulthood showed the most dramatic response. If the onset of the illness was before age 17 the response to treatment was slower and most treatment failure occurred in this group of grown-up childhood schizophrenics. Patients who were either too regressed or ill to cooperate on an outpatient basis were treated in hospital for an average of six weeks with a short series of ECT.

Improvement was rated by:
(a) Patients' subjective statements
(b) Family observations
(c) Psychiatric evaluation
(d) Decrease in HOD scores

Of the group 71 percent improved. The greatest response was made by the 70 patients who were both alcoholic and schizophrenic.


Dr. Cott's article ran between pages 44 and 60, not 44 to 49 as the committee erroneously wrote.

After describing in clinical detail the diagnostic criteria and treatment program, Dr. Cott presented six detailed case histories of children he had treated. As a pioneer in the treatment of children, Dr. Cott's views must be taken very seriously. He concluded, "The response to the nicotinic acid treatment is slow and in my experience three to six months is the minimum time during which significant changes become manifest. Most parents have reported that the first noticeable change is a slowing of the hyperactivity and attendant on this slowing, a willingness to learn."

"Although much work and research will be required to fill the gaps remaining in our knowledge of schizophrenia, we can be encouraged with the accomplishments achieved in less than two decades in treating this dread illness. We can offer hope to those who suffer its ravages and to the parents of children whose potential is destroyed so early."

(6) Schizophrenia: Responsive to Intensive Hospital Treatment as Monitored by the HOD and OIT tests, F. Chiossone, D. R. Hawkins, F. Furfaro, and R. P. Runyon (1969)

Over a 10-month period, 140 patients were admitted into the psychiatric division of Brunswick Hospital Center. ECT was given to 85 patients. This group responded as follows:

- unimproved: 2
- improved: 118
- much improved: 12
- very much improved: 6
- recovered: 2

The authors concluded, "Intensive short-term hospital treatment for schizophrenia proved to be highly effective in bringing about substantial improvement in the great majority of patients and this improvement was substantiated by objective testing." The committee ignored this report.

(7) Subclinical Pellagra: Its Diagnosis and Treatment, R. G. Green (1970)

A discussion and presentation of a few cases to demonstrate the response of...
these patients with learning and behavioral disorders to vitamin 133 The committee ignored this report

(8) How One Psychiatrist began Using Niacin, H. L. Newbold (1970). This is an excellent account, ignored by the committee, in which a skillful psychiatrist describes his history which led him becoming an orthomolecular psychiatrist. Most psychiatrists would be unwilling to expose themselves to such pressure from their antivitamin colleagues.

(9) The Use of Megavitamin Therapy in Regulating Severe Behavior Disorders, Drug Abuses and Frank Psychoses, G. Von Hilsheimer, S. D. Klotz, G. McFall, H. L. Newbold, A. Van West, and D. Quirk (1971). These investigators treated 32 patients between September 1967 and September 1969 in acute psychotic episodes or in the aftermath of acute crises which did not appear to be psychotic in nature, not related to drug abuse. The patients were given up to 24 g of niacin per day.

"All these patients have responded with reduced dysphoria, subjective reports of improved feeling states, improved perception, control of behavior and general improvement in tonus, orientation and appearance of health."

"Several severe psychotic patients seem to have recovered as a direct function of niacin therapy." The committee ignored this report.

(10) A Report on the Use of Orthomolecular Therapy in a California State Hospital, E. R. LeClair (1972). E. R. LeClair described results of treating 30 male schizophrenics in a state mental hospital. She was permitted to do so after she was able to demonstrate the effect of orthomolecular therapy on six psychotic patients. They were too disorientated and agitated to participate in psychotherapy and had failed to respond to the committee's favorite therapy—tranquilizers. This was a test project since, according to the hospital staff, vitamin therapy "has already been proven not to work." Of the six, three were in almost constant restraints or seclusion of one kind or another. Five had been in hospital one month and the sixth for seven. They had as a group been in hospital 18 times, averaging 8.5 months per patient. The mean HOD total score was 144.5 indicating very severe psychosis. The average for all schizophrenics is around 70. Each patient responded. They became more manageable, less agitated, less hostile, less aggressive. They began to talk and became more sociable. Hallucinations and delusions diminished. These observations by patient, family, and staff were confirmed by a decrease in the HOD scores to a mean of 4.8 in 2.4 months. (Normal scores range from 0 to 15.) Four were discharged with no tranquilizers and two on tranquilizers, but the doses were much smaller. After six months only one was still on tranquilizers. Five remained well after discharge. The sixth discontinued his vitamins and was rehospitalized three times in 10 months. As each patient was discharged, another was placed on the same program. Eventually another 24 were treated with similar results.

Another 14 were started, but could not be continued because one was discovered to have a medical problem, six were transferred to another hospital, and one was discharged by the court. Two were transferred to a private hospital, in three patients new physicians would not permit vitamins to be continued, and in one emesis of niacin and niacinamide was unavoidable. While on vitamins for a brief period, 11 of the 14 showed some improvement. Ten are still in hospital.

Summary of Results:

Hospital experience before vitamins—3.43 times for 10.47 months calculated for all 30 (per person)

Excluding seven never in hospital values were 4.48 for 13.65 months.

Discharge—19 to themselves; seven to parents; four to board and care facility.
Follow-up—When the paper was prepared 28 were evaluated. Twenty remained on megavitamin therapy. Of the eight not on vitamins six had been rehospitalized one to five times in the following 10 months. One committed suicide and one maintained himself on phenothiazines. Three were ordered by their physicians to discontinue vitamins. Of the 28, 19 were gainfully employed, five were in board and care facilities, two retired, and one was dead. Five were on welfare assistance compared to 18 before treatment started.

The author noted, "A discouraging aspect of the project was the poor reception by many of the hospital personnel. The security and complacency in tradition were apparent. The program director, who gave permission for the project, experienced many uncomplimentary comments from his fellow psychiatrists. Several physicians also placed patients on 100 mg to 300 mg of niacin and ascorbic acid. When no improvement was noted within two to four weeks, they boastfully made it known that the 'vitamins did not work for them.' Had they done it double blind using these totally inadequate doses we are certain the committee would have given them ample space in their report.

The committee ignored this study.


Subjects were 100 children diagnosed as suffering from brain dysfunction. They were divided into four groups:

(a) 41 Ss (28 boys, 13 girls) who received neurological organization (NO) only
(b) 14 Ss (6 boys, 8 girls) NO only
(c) 14 Ss (10 boys, 4 girls) NO and megavitamin therapy (MV)
(d) 24 Ss (18 boys, 6 girls) NO and MV

For groups (a) and (b) there was no significant gain in the neurological quotient (NQ), but for groups (c) and (d) there was a significant improvement in NQ.

They concluded, "In any event, the fact that megavitamin treatment was associated with significant results in this study justifies further research into this type of therapy." This paper was ignored by the committee.


This is a general outline of treatment including treatment of children allergic to foods.


This is one of the first accounts of the role of allergies in producing mental illness. An explanation for schizophrenics' failure to respond to megavitamins is now available. Why should a patient who is psychotic because he is consuming milk to which he is allergic, respond to vitamins?

(14) Pyridoxine and Trace Element therapy in Selected Clinical Cases, P. Cutler (1974).

The use of trace elements is rapidly expanding.


This is a general review paper of orthomolecular treatment based upon treatment of 500 children between 1966 and 1971.


Using a comprehensive treatment approach under the medical model, Dr. Hawkins' Clinic treated over 4,000 patients. At this Long Island Clinic they carry a case load of 1,500 patients for $300,000 per year. Many are chronic schizophrenics with repeated admissions to hospital. Their results were superior to...
any they had seen with standard psychiatric treatment and cost averaged to $200 per year per patient.

One family agency, the Council for Youth Services of the Episcopal Diocese of Long Island, had become bogged down with long waiting lists and shortage of staff. When they converted to the new system, they soon eliminated a waiting list, doubled their case load, and solved their financial problems. The committee ignored this paper.

(17) A First Evaluation, M. Williams (1971)

"I was trained in orthodox analytical treatment methods and applied these in my practice for 15 years."

"I discovered that results of strictly psychoanalytical therapy with or without combined chemical (tranquilizer) therapy produced poor recovery and remission percentages in schizophrenic patients."

"After three years of using these diagnostic and treatment procedures (orthomolecular—our note) I have compiled sufficient case histories upon which to base my own conclusions. My first impression was the number of unrecognized schizophrenics. Almost 50 percent of previously diagnosed neurotics were actually suffering from schizophrenia. History usually indicated lifelong problems, and early recognition and orthomolecular treatment, in some cases accompanied by supportive psychotherapy, brought about rapid response."

"Chronic (long-standing) schizophrenic patients do not respond as quickly or as well. However, I have noted marked improvement in even the most chronic cases." This report was ignored by the committee.

(18) Clinical Impressions in Early and Chronic Schizophrenia and Diagnostic Procedures, M. Williams (1972)

Dr. Williams presented three cases to illustrate the response to treatment. This report was ignored by the committee.

(19) Does Acid Well Water Erode Plumb-
C. Pfeiffer, U. Iliev (1972) See also Pfeiffer, Iliev, and Goldstein (1973)
Both papers are ignored by the committee

Dr. Vajay treated 89 outpatients in private practice between October 1970 and December 31, 1971. By then 23 had "graduated" away from drugs and four months later the number increased to 27.
This was a chronic group, the most frequent ages being 19, 20, and 21.
Duration of addiction varied from six to 84 months. Only 17 used one drug. The rest were primarily on heroin, but combined it with three or more other drugs. None had ever been treated with methadone, 14 had been treated once, seven, twice, 20, three times, and 34, four times, and five had been in and out five to 10 times.
There was a very high rate of physical illness. 68 had orthostatic hypotension, 50 chronic bronchitis and nasopharyngitis, 52 had pustular acne, 48 acute thrombophlebitis of anecubital or dorsal veins of hands, 23 had chronic prostatitis (nine due to gonorrhea), 11 women had pelvic inflammatory disease (10 had gonorrhea). Twenty developed hepatitis during treatment. Eight had ulcerative colitis, one duodenal ulcer, and one chronic asthma.
All were also suffering from a variety of psychiatric illnesses. One was manic depressive, one epileptic with psychosis following brain trauma, two were organic brain syndromes, and 35 were schizophrenic borderline or pseudoneurotic.
Twenty-six were given 5 g buffered nicotinic acid, 1 g of ascorbic acid, and 1 mg of vitamin B12 plus 15 mg of vitamin B6 by injection every four days. They were all started on methadone 40 mg per day for 30 days. This was then gradually reduced until they graduated off it. They also received individual psychotherapy. Group therapy was quickly rejected.
For such a severely sick group the results were very encouraging. Out of the 27 graduates, 17 were schizophrenic and 22 were on megadose vitamins. He concluded, "in this 14-month program, low-dose methadone is enough for maintenance, that the immediate flush of nicotinic acid successfully replaces the 'heroin' high and is a useful tool to maintain motivation and keep the patient free from craving for heroin."
The committee ignored this paper.

(25) Nicotinic Acid Therapy in Chronic Schizophrenia, Sehden and Olson (1974)
These authors treated 14 chronic schizophrenic patients with 3 g per day of nicotinic acid for 90 days and compared their progress with 13 untreated patients. Every patient had been on a plateau at their current level for six months. Of the nicotinic acid group two were much improved and four made minimal to moderate improvement. Out of the placebo group one was much improved and one moderately improved. For this distribution, Chi Sq = 2.5. The probability this is due to chance is about 12 percent. However, it is a very small sample. Had the sample been twice as large with the same distribution Chi Sq. would have been over five which would reduce the probability to 2 percent.
However, these authors were so convinced nicotinic acid could not work they muddled around in their conclusion. Surely the improvement of six out of 14 chronic patients who had shown no change in six months should have alerted them that there might be something there. They could as easily have expanded their series. This is the reason why the motivation of an experimenter is important. An investigator wishing to negate findings will run his experiments in such a way as to maximize the negative effect while an experimenter hoping to corroborate will run his experiments longer and may then find the positive results. The first investigator will always quit when he is ahead because he minimizes the danger of being proven wrong by his own data. The corroborator may also be disappointed, but by persevering he at least
greatly increases the probability he will be a party to the introduction of something useful and novel. The committee were all hoping to destroy the megavitamin claims. They, therefore, conducted their literature review in a way designed to maximize this hoped-for event.

(26) Pfeiffer, Sohler, Jenney, and Iliev (1974) confirmed our original description of malvaria (Hoffer and Osmond, 1963). A more appropriate term in our opinion is pyrroluria, the term coined by Pfeiffer. The patient who excretes too much kryptopyrrole (hereafter KP), i.e., has too much in his body, has the following characteristics: (1) white spots in the nails; (2) failure to remember dreams; (3) sweetish breath odor; (4) left upper quadrant abdominal pain; (5) dysperceptive schizophrenia and neurological metabolic symptoms. KP combines with pyridoxine and zinc to produce symptoms of pyridoxine and zinc deficiency. Adequate doses of pyridoxine, up to 3 g per day, and zinc will relieve the symptoms.

(27) Pfieffer (1974) In this report Pfieffer summarized his work leading to a division of schizophrenics into several biochemical types, i.e., histapenics, histadelics, and pyrroluriacs. The specific biochemical treatment for each group is outlined.

(28) Cott (1973) Here Dr Cott reported his conclusions based upon a series of 500 children tested over a seven-year period. He concluded that a large number of disturbed children and children with learning disabilities can be helped by orthomolecular treatment. This paper came out after the APA Task Force Report, but they would undoubtedly have ignored it since it did not follow the fad double-blind methodology.

(29) Mickelson (1975) reported the case of a 21-year-old male schizophrenic who did not respond to any of the committee's favorite treatments including counseling, milieu therapy (three months) in a general hospital psychiatric unit, three weeks of day therapy, the usual gamut of major tranquilizers, and a series of 6 ECT, a rehabilitation program, and frequent visits to a social worker. This was followed by six additional weeks in a psychiatric ward from which he was almost forcibly discharged and admission soon after to a mental hospital. It is clear that this unfortunate patient had not responded and was doomed to the usual pattern of the chronically tranquilized patient—the usual revolving door between community and hospital or hospital surrogate.

But the parents had read our book, How To Live With Schizophrenia, took their son out against medical advice and had him sent to an orthomolecular psychiatrist far from home. On discharge from this latest treatment he was greatly improved.

One would think that most reasonably curious psychiatrists would become interested. Dr. Mickelson, who carefully reported how the most persuasive techniques known including milieu therapy and the other psychotherapies had failed to do anything, now falls back on the old, never established notion that the patient improved because of the parents' faith in the biochemical approach. That is, the recovery arose from a powerful placebo effect operating from a distance of several hundred miles.

(30) Rimland, Dreyfus, and Callaway (1976) completed a double-blind controlled experiment on 16 autistic type children who had shown noticeable behavioral improvement when given pyridoxine (up to 3 g per day). The patients were also taking other nutrient supplements. The pyridoxine supplement was replaced during two separate experimental trial periods: first by substance A, then by B. The first two authors assigned behavioral ratings to the experimental trials after which the third author revealed which substance was pyridoxine. It was identified correctly in 11 out of 15 children.
For the 16th child the judges could see no difference. It was then learned that pyridoxine had been given for both A and B periods. This is one of the best types of double blinds for a group homogeneous with respect to their response to pyridoxine was used. Secondly pyridoxine, contrary to nicotinic acid, does not give itself away by producing a flush.

In the spring of 1974 the Canadian SchizophreniaJoundation held its third annual meeting. It was entirely devoted to orthomolecular treatment and was published in the journal of Orthomolecular Psychiatry, 1974, December issue. It is available from the Canadian Schizophrenia Foundation, Regina, Saskatchewan, as a "Primer on Orthomolecular Treatment."
OPINION AND COMMENT

On the Orthomolecular Environment of the Mind: Orthomolecular Theory
By Linus Pauling, Ph.D.

The author defines orthomolecular psychiatry as the achievement and preservation of good mental health by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body, such as the vitamins. He states that there is sound evidence for the theory that increased intake of such vitamins as ascorbic acid, niacin, pyridoxine, and cyanocobalamin is useful in treating schizophrenia. The negative conclusions of APA Task Force Report 7, Megavitamin and Orthomolecular Therapy in Psychiatry, he says, result not only from faulty arguments and from a bias against megavitamin therapy but also from a failure to deal fully with orthomolecular therapy in psychiatry. Three psychiatrists comment on Or Pauling's presentation.

Orthomolecular Psychiatry is the achievement and preservation of mental health by varying the concentrations in the human body of substances that are normally present, such as the vitamins. It is part of a broader subject, orthomolecular medicine, an important part because the functioning of the brain is probably more sensitively dependent in its molecular composition and structure than is the functioning of other organs.

After having worked for a decade on the hereditary hemolytic anemias, I decided in 1954 to work on the molecular basis of mental disease. I read the papers and books dealing with megavitamin therapy of schizophrenia by Hoffer and Osmond (2-4) as well as the reports on studies of vitamins in relation to mental disease by Cleckley and Sydenstricker (5-6) and others. In the course of time I formulated a general theory of the dependence of function on molecular structure of the brain and other parts of the body and coined the adjective "orthomolecular" to describe it.

There is no doubt that the mind is affected by its molecular environment. The presence in the brain of molecules of LSD, mescaline, or some other schizophrenogenic substance is associated with profound psychic effects. Mental manifestations of avitaminosis have been reported for several vitamins. A correlation between behavior of schoolchildren with concentration of ascorbic acid in the blood (increase in "alertness" or "sharpness" with increase in concentration) has been reported by Kubala and Katz (7). A striking abnormality in the urinary excretion of ascorbic acid after an oral loading dose was reported for chronic schizophrenics by VanderKamp (8) and by Herjanic and Moss-Herjanic (9). My associates and I (10) carried out loading tests for three vitamins on schizophrenic patients who had recently been hospitalized and on control subjects. The percentage of schizophrenic patients who showed low urinary excretion of each vitamin was about twice as great as that of the controls: for ascorbic acid, 74 percent of the schizophrenic patients showed low urinary excretion versus 32 percent of the controls; for niacinamide, 81 percent versus 46 percent; and for pyridoxine, 52 percent versus 24 percent. The possibility that the low values in urinary excretion of these vitamins for schizophrenic patients resulted from poor nutrition is made unlikely by the observation that the numbers of subjects low in one, two, or all three vitamins corresponded well with the numbers calculated for independent incidence.

There are a number of plausible mechanisms by which the concentration of a vitamin may affect the functioning...
of the brain. One mechanism, effective for vitamins that serve as coenzymes, is that of shifting the equilibrium for the reaction of apoenzyme and coenzyme to give the active enzyme. An example is the effectiveness of cyanocobalamin (vitamin B12) given in amounts 1,000 times greater than normal to control the disease methylmalonic aciduria (11-14). About half of the patients with this disease are successfully treated with megadoses of vitamin B12. In these patients a genetic mutation has occurred and an altered apoenzyme that has a greatly reduced affinity for the coenzyme has been produced. Increase in concentration of the coenzyme can counteract the effect of the decrease in the value of the combining constant and lead to the formation of enough of the active enzyme to catalyze effectively the reaction of conversion of methylmalonic acid to succinic acid.

In the human population there may be several alleles of the gene controlling the manufacture of each apoenzyme; in consequence the concentration of coenzyme needed to produce the amount of active enzyme required for optimum health may well be somewhat different for different individuals. In particular many individuals may require a considerably higher concentration of one or more coenzymes than other people do for optimum health, especially for optimum mental health. It is difficult to obtain experimental evidence for gene mutations that lead to only small changes in the properties of enzymes. The fact that genes that lead to large and more easily detectable changes in the properties of enzymes occur, as in individuals with methylmalonic aciduria, for example, suggests that mutations that lead to small changes also occur.

Significant differences in enzyme activity in different individuals have been reported by many investigators, especially by Williams (15) who has made many studies of biochemical individuality. It is likely that thorough studies of enzymes would show them to be similar to the human hemoglobins. A few of the abnormal human hemoglobins, most of which involve only the substitution of one amino-acid residue for another in either the alpha chain or the beta chain of the molecule, differ greatly in properties from normal adult hemoglobin, leading to serious manifestations of disease.

It was in the course of the study of one of these diseases, sickle cell anemia, that the first abnormal hemoglobin was discovered (16). Most of the abnormal human hemoglobins, however, differ from normal hemoglobin in their properties to only a small extent, so that there is no overt manifestation of disease. There is, nevertheless, the possibility that even the small changes in properties of an abnormal hemoglobin associated with a mild hemoglobinopathy will have deleterious consequences. An example is the intolerance to sulfa drugs associated with the substitution of arginine for histidine in the locus 58 in the alpha chain or 63 in the beta chain. It is likely that individual differences in enzyme activity will in the course of time be shown to be the result of differences in the amino-acid sequences of the polypeptide chains of the apoenzymes.

More than 100 abnormal human hemoglobins are now known, and the human population may be expected to be similarly complex with respect to many enzymes, including those involved in the functioning of the brain. A tendency to schizophrenia is probably polygenic in origin. I have suggested (1) that the genes primarily involved in this tendency may well be those which regulate the metabolism of vital substances such as the vitamins.

Some vitamins are known to serve as coenzymes for several enzyme systems. We might ask if the high concentration of coenzyme required to produce the optimum amount of one active enzyme might not lead to the production of far too great an amount of another active enzyme. The answer to this question is that the danger is not very great. For most enzymes the concentration of coenzyme and the value of the comb
ination constant are such that most (90 percent or more) of the protein is converted to active enzyme. Accordingly, a great increase in concentration would increase the amount of most active enzymes by only a few percentage points, whereas it might cause a great increase for a mutated enzyme.

The Orthomolecular Treatment of Schizophrenia

In the book Orthomolecular Psychiatry: Treatment of Schizophrenia (17) my colleagues and I pointed out that the orthomolecular treatment of schizophrenia involves the use of vitamins (megavitamin therapy) and minerals; the control of diet, especially the intake of sucrose; and, during the initial acute phase, the use of conventional methods of controlling the crises, such as the phenothiazines. The phenothiazines are not, of course, normally present in the human body and are not orthomolecular. However, they are so valuable in controlling the crisis that their use is justified in spite of their undesirable side effects.

Hawkins (18, p. 640) stated that his initial combination of vitamins for the treatment of schizophrenia was 1 gm of ascorbic acid, 1 gm of niacinamide, 50 mg of pyridoxine, and 400 I. U of vitamin E four times a day. Other vitamins may also be given. A larger intake, especially of niacinamide or niacin, may be prescribed; the usual amount seems to be about 8 gm a day after an initial period of 4 gm a day.

The vitamins, as nutrients or medications, pose an interesting question. The question is not, Do we need them? We know that we do need them, in small amounts to stay alive. The real question is, What daily amounts of the various vitamins will lead to the best of health, both physical and mental? This question has been largely ignored by medical and nutritional authorities.

Let us consider schizophrenia. Osmond (19, p 200) stated that about 40 percent of schizophrenics hospitalized for the first time are treated successfully by conventional methods in that they are released and not hospitalized a second time. The conventional treatment fails for about 60 percent in that the patient is not released or is hospitalized again.

Conventional treatment includes a decision about vitamin intake. Usually it is decided that the vitamins in the food will suffice or that a multivitamin tablet will also be given. The amounts of ascorbic acid, niacin, pyridoxine, and vitamin E may be approximately the daily allowances recommended by the Food and Nutrition Board of the U.S. National Academy of Sciences-National Research Council: 60 mg of ascorbic acid, 20 mg of niacin, 2 mg of pyridoxine, and 15 I. U of vitamin E. Is this amount of vitamins correct? Would many schizophrenic patients respond to their treatment better if the decision were made that they should receive 10 or 100 or 500 times as much of some vitamins? What is the optimum intake for these patients? I believe there is much evidence that the optimum intake for schizophrenic patients is much larger than the recommended daily allowances. By the use of orthomolecular methods in addition to the conventional treatment of schizophrenia, the fraction of patients hospitalized for the first time in whom the disease is controlled may be increased from about 40 percent to about 80 percent.

Ascorbic Acid

It was reported by Horwitt in 1942 (20) and by later investigators that schizophrenic patients receiving the usual dietary amounts of ascorbic acid had lower concentrations of ascorbic acid in the blood than people in good health. The loading-test results of VanderKamp (8), Herjanic and Moss-Herjanic (9), and Pauling and associates (10) have been mentioned above. In his discussion of ascorbic acid and schizophrenia, Herjanic (21) concluded:
The individual variation of the need for ascorbic acid may turn out to be one of the contributing factors in the development of the illness. Ascorbic acid is an important substance necessary for optimum functioning of many organs. If we desire, in the treatment of mental illness, to provide the "optimum molecular environment," especially the optimum concentration of substances normally present in the human body (Pauling, 1968 [1]), ascorbic acid should certainly be included (21, p 314).

There is, moreover, a special reason for an increased intake of ascorbic acid by patients with schizophrenia or any other disease for which there is only partial control. About 60 mg of ascorbic acid a day is enough to prevent overt manifestations of avitaminosis C (scurvy) in most people. However, there are several significant arguments to support the thesis that the optimum intake for most people is 10 to 100 times more than 60 mg. These arguments are summarized in the papers and books of Irwin Stone (22) and myself (23, 24). They constitute the theoretical basis for the customary use of about 4 gm of ascorbic acid a day in the orthomolecular therapeutic and prophylactic treatment of schizophrenia.

A significant controlled trial of ascorbic acid in chronic psychiatric patients was reported in 1963 by Milner (25). The study, which was double-blind, was made with 40 chronic male patients: 34 had schizophrenia, 4 had manic-depressive psychosis, and 2 had general paresis. Twenty of the patients, selected at random, received 1 gm of ascorbic acid a day for three weeks; the rest received a placebo. The patients were checked with the Minnesota Multiphasic Personality Inventory (MMPI) and the Wittenborn Psychiatric Rating Scales (WPRS) before and after the trial. Milner concluded that "statistically significant improvement in the depressive, manic, and paranoid symptom-complexes, together with an improvement in overall personality functioning, was obtained following saturation with ascorbic acid" (25). He suggested that chronic psychiatric patients would benefit from the administration of ascorbic acid.

We found (10) that of 106 of the schizophrenic patients we studied who had recently been hospitalized in a private hospital, a county-university hospital, or a state hospital, 81 (76 percent) were deficient in ascorbic acid, as shown by the six-hour excretion of less than 17 percent of an orally administered dose. Only 27 of 89 control subjects (30 percent) showed this deficiency. Great deficiency (less than 4 percent excreted) was shown by 24 (22 percent) of the schizophrenic subjects and by only 1 (1 percent) of the controls. I have no doubt that many schizophrenic patients would benefit from an increased intake of ascorbic acid. My estimate is that 4 gm of ascorbic acid a day, in addition to the conventional treatment, would increase the fraction of acute schizophrenics in whom the disease is permanently controlled by about 25 percent. Except for that of Milner (25), no controlled trial of ascorbic acid in relation to schizophrenia has been made, so far as I know.

The requirement of niacin (nicotinic acid) for proper functioning of the brain is well known. The psychosis of pellagra, as well as the other manifestations of this deficiency disease, is prevented by the intake of a small amount of niacin, about 20 mg a day. In 1939 Cleckley, Sydenstricker, and Geeslin (5) reported the successful treatment of 19 patients with severe psychiatric symptoms with niacin, and in 1941 Sydenstricker and Cleckley (6) reported similarly successful treatment of 29 patients with niacin. In both studies, moderately large doses of niacin, 0.3 to 1.5 gm a day, were given. None of the patients in these studies had physical symptoms of pellagra or any other avitaminosis. A decade later, Hoffer and Osmond (2, 3) initiated two double-blind studies of niacin or niacinamide in the treatment of schizophrenia. Another double-blind study was reported by Denson in 1962 (26). In 1964 Hoffer and
Osmond (4) reported that a 10-year follow-up evaluation of the patients in their initial studies showed that 75 percent had not required hospitalization, compared with 36 percent of the comparison group, who had not received niacin. Similar estimates have been made by Hawkins (18, p 585). There are, however, contradictory statements by other investigators. The question of the weight of the evidence is discussed below in the section on the APA Task Force report.

Pyridoxine

Pyridoxine, vitamin B6, is used in the treatment of schizophrenia in amounts of 200 to 800 mg a day by many ortho-molecular psychiatrists. Derivatives of this vitamin are known to be the coenzymes for over 50 enzymes, and the chance of a genotype with need for a large intake of the vitamin is accordingly great. There is evidence that pyridoxine is involved in tryptophan-niacin metabolism.

A double-blind placebo-controlled study had been made of pyridoxine and niacin by Ananth, Ban, and Lehmann (27). Their experimental population consisted of 30 schizophrenic patients: 15 were men, 15 were women, their mean age was 41.7 years, and their mean duration of hospitalization was 10.9 years. They were randomly assigned to three treatment groups: 1) the combined treatment group, which received 3 gm of nicotinic acid a day for 48 weeks and 75 mg of pyridoxine a day during three 4-week periods; 2) the nicotinic acid group, which received 3 gm of nicotinic acid a day for 48 weeks and a pyridoxine placebo; and 3) the pyridoxine group, which received 75 mg of pyridoxine a day during three 4-week periods and a nicotinic acid placebo. In addition, neuroleptic preparations were administered according to clinical requirements for the control of psychopathology. The investigators reported that "of the ten patients in each treatment group, seven improved and three deteriorated in the nicotinic acid group, nine improved and one deteriorated in both the combined treatment group and in the pyridoxine group" (27). They also stated:

Of the three indices of therapeutic effects, global improvement in psychopathology (Brief Psychiatric Rating Scale and Nurses Observation Scale for Inpatient Evaluation) scores was seen in all three groups; the number of days of hospitalization during the period of the clinical study was lower in both the nicotinic acid and the combined treatment group; and only in the combined treatment group was the daily average dosage of phenothiazine medication decreased. Thus, improvement in all three indices was noted in the combined treatment group.

However, several side effects were observed during the therapeutic trials, indicating that the vitamins used are not completely safe (27, p 381). The investigators reached the conclusion that "on balance, these results suggest that the addition of pyridoxine may potentiate the action of nicotinic acid. Thus pyridoxine seems to be a useful adjunct to nicotinic acid therapy" (27, p 381); Hawkins (18) commented on this work in the following way:

The therapeutic effect was demonstrable even though the patients had been hospitalized for an average of 10.9 years, were not on hypoglycemic diets, and the doses of both pyridoxine (75 mg daily) and vitamin B3 (3 gm a day) were considerably below the dosages we routinely prescribe (18, p 638).

Cyanocobalamin

A deficiency in cyanocobalamin (vitamin B12), whatever its cause, leads to mental illness as well as to such physical manifestations as anemia. The anemia can be controlled by a large intake of folic acid, but the mental illness and neurological damage cannot. A pathologically low concentration of cyanocobalamin in the blood serum has been reported to occur in a much larger percentage of patients with mental illness than in the general population. Edwin and associates (28) determined the
amount of vitamin B12 in the serum of every patient over 30 years old admitted to a mental hospital in Norway during a period of one year. Of the 396 patients, 61 (15.4 percent) had a subnormal or pathologically low concentration of vitamin B12, less than 150 pg per ml (the normal range is 150 to 1,300 pg per ml). This incidence is 30 times as great as that estimated for the population as a whole. Other investigators have reported similar results and have suggested that a low serum concentration of vitamin B12, whatever its origin, may cause mental illness. In addition, of course, mental illness may accompany some genetic diseases, such as methylmalonic acidemia, which can be controlled only by achieving a serum concentration of cyanocobalamin far greater than normal.

Minerals and Other Vitamins

There is some evidence that mental illness may result from deprivation of or abnormal need for minerals and other vitamins (see, for example, Pfeiffer, 111ev, and Goldstein [29]). Further work in this field by psychiatrists and biochemists is needed.

THE APA TASK FORCE REPORT

In July 1973 an APA task force of five physicians and one consultant issued a 54-page report titled Megavitamin and Orthomolecular Therapy in Psychiatry (30). In this report the Task Force on Vitamin Therapy in Psychiatry purports to present both theoretical and empirical reasons for completely rejecting the basic concept of orthomolecular psychiatry, which is the achievement and preservation of good mental health by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body.

Some Errors in the Report

It is mentioned in the report that in the treatment program of the orthomolecular psychiatrists "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" (p. 46). The assumption is made by the task force that the optimum intake of vitamins for mental health is the conventional average daily nutritional requirement, with growth and development as the criteria: "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" (p. 40). Mention is made in the report of the well-known genetic diseases with both psychic and somatic manifestations that can be controlled by an intake of a vitamin 100 or 1,000 times the usually recommended daily allowance, but the possibility that less obvious genetic differences could result in an increased individual need for a larger intake of vitamins in order to achieve good mental health, as discussed in my 1968 publication (1) and in the earlier sections of this paper, is rejected on the basis of arguments that have little value or pertinence.

One such argument is the following:

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 [nicotinamide], 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.

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 (pp. 40-42).
There is an obvious error in this task force argument. There is no incompatibility between two functions of nicotinic acid; some molecules may engage in one function and others in the other. A defect in either function might be controlled by increasing the intake of the vital substance. A "double deficit" is not needed. The authors of the report would have seen the fallacy in their argument if they had set up some equilibrium and reaction rate equations, as was done in my 1968 paper (1).

The task force expresses an interesting misunderstanding of the nature of vitamins, in the following words: "By common definition a vitamin is not only an essential nutrient, but it is essential because it is transformed into a co-enzyme vital for metabolic reactions" (p. 41). In fact, this is not the common definition of a vitamin; it is wrong. Some vitamins, including vitamin C, are not known to be transformed into a co-enzyme. This misunderstanding by the task force may have contributed to the misinterpretation of the evidence for and the theoretical basis of orthomolecular psychiatry.

Nicotinic acid as a methyl acceptor is referred to in the report: "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" (p. 16). In fact, the molecular weights of nicotinic acid and methionine (a methyl donor) are nearly the same, 123 and 149, respectively. Instead of 3 gm, 16.5 gm of nicotinic acid would have had to be given each day to accept the methyl groups donated by the 20 gm of methionine that was given each day. The study referred to as number 12 (31), which resulted in an exacerbation of the illness of 30 schizophrenic patients who participated in it, has no value as a test of the methyl acceptor theory of nicotinic acid. Consideration of ethical principles may have kept the investigators from repeating the study with use of the proper equimolar amounts of nicotinic acid and methionine.

The Failure to Discuss Ascorbic Acid and Pyridoxine

In several places the AM task force report mentions the use of 1 to 30 gm of ascorbic acid a day by orthomolecular psychiatrists. There are, however, no references to the literature. Milner's double-blind study (25) is not mentioned, nor is there any discussion of the many papers in which a low level of ascorbic acid in the blood of schizophrenics was reported. Neither the general theory of orthomolecular psychiatry, as presented in my 1968 paper (1), nor any of the special arguments about the value of ascorbic acid is presented or discussed in any significant way. There is, moreover, no discussion in the report of pyridoxine and no reference to the 1973 work by Ananth, Ban, and Lehmann (27) on the potentiation by pyridoxine of the effectiveness of niacin in controlling chronic schizophrenia. The title of the report, Megavitamin and Orthomolecular Therapy in Psychiatry, is completely inappropriate, and the general condemnation of megavitamin and orthomolecular therapy is unjustified.

Niacin

The report does say that it is possible that the other water-soluble vitamins will prove to be more effective than niacin, but it adds: 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 (p. 46).

I shall point out below that the principles of medical ethics prevent
orthomolecular psychiatrists from withholding from half of their patients a treatment that they consider to be valuable. Controlled tests can be carried out only by skeptics. I now ask whether the task force is justified in saying that the massive use of niacin has been proved to have no value when it is employed as the sole variable along with conventional treatments of schizophrenia. My answer to this question, from a study of the evidence quoted in the report, is that it is not justified.

The evidence that niacin has no value is far from conclusive. A beneficial effect of niacin or niacinamide was reported for three double-blind studies (two by Hoffer and Osmond and their collaborators [2, 3, 32] and one by Denson [26]) and in 12 open clinical trials by other investigators referred to in the report. On the other hand, the report mentions 7 double-blind studies in which a statistically significant difference between the niacinamide subjects and the controls was not observed.

A failure to reject with statistical significance the null hypothesis that the treatment and the placebo have equal value is not proof that the treatment has no value. The explicit statistical analysis of an alternative hypothesis should be carried out: for example, the hypothesis that there is a 10-percent or 20-percent greater improvement in the treated subjects than in the placebo subjects. No such analysis has been published.

In fact, some of the "negative" studies indicate that the treatment has value. The report states that "Greenbaum [33] 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" (p. 11). It is true that no statistically significant differences were seen, but that is not the whole truth. The principal criterion of improvement in this study was the increase in the score on a clinical scale of observable behavior categories. The average improvement in the score of the 17 children receiving niacinamide was 4.0 units and that of the 24 controls was 2.6 units (there was a third group of 16 children who were given a tranquilizer and niacinamide). The children who were given niacinamide showed a 54-percent greater improvement than the children who were given placebo. The groups were too small, however, for the difference to be significant at the 95-percent level of confidence. This study does not prove that niacinamide has no value. Rather it indicates that niacinamide has greater value than the placebo, even though it fails to show this at the customary level of statistical significance.

The Hoffer-Osmond Diagnostic Test

Two-thirds of the report relates to niacin, and one-third to the Hoffer-Osmond Diagnostic Test (HOD) [34], which has no special connection with megavitamin or orthomolecular psychiatry except that it was devised by the originators of niacin therapy. The report should have been given the title Niacin Therapy and the HOD Test, or published as two reports, one on niacin and one on the HOD test. It would have been still better for the task force to have discussed megavitamin and orthomolecular therapy in psychiatry fully.

The Question of Controlled Experiments

The report refers to the low credibility of the megavitamin proponents, whose published results were not duplicated in studies carried out by one of the task force members (p. 48). The penultimate sentence of the report is, "Their credibility is further diminished by the consistent refusal over the past decade to perform controlled experiments and to report their new results in a scientifically acceptable fashion" (p. 48).

I have talked with the leading orthomolecular psychiatrists and have found that they feel the principles of medical
ethics prevent them from carrying out controlled clinical tests, with half of their patients receiving orthomolecular therapy in addition to the conventional treatment and the other half receiving only the conventional treatment. It is the duty of the physician to give to every one of his patients the treatment that in his best judgment will be of the greatest value. Some psychiatrists, including Hoffer and Osmond, carried out controlled trials 20 years ago. They became convinced that orthomolecular therapy, along with conventional treatment, was beneficial to almost every patient. From that time on their ethical principles have required that they give this treatment and not withhold it from half of their patients. The task force is wrong in criticizing the orthomolecular psychiatrists for not having carried out controlled clinical trials during the last few years. Instead, it is the critics, who doubt the value of orthomolecular methods, who are at fault in not having carried out well designed clinical tests.

It is also the duty of a physician to give to a patient a treatment that may benefit him and is known not to be harmful. The incidences of toxicity and other serious side effects of the doses of vitamins used in orthomolecular medicine are low. There is significant evidence that an increased intake of certain vitamins may benefit the patient. It is accordingly the duty of the psychiatrist to prescribe these vitamins for him.

The Bias of the Task Force

The last sentence of the report reads as follows:

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 (p 48). This sentence, like others in the report, shows the presumably unconscious bias of the task force "Promulgate" (misused here) is a pejorative word, and "catch phrases" is a pejorative expression. I do not understand why megavitamin therapy and orthomolecular treatment should be called misnomers. This concluding sentence, like many others in the book, seems to me to have been written in order to exert an unjustifiably unfavorable influence on the readers of the report.

I have written two popular books, No More War! (35) and Vitamin C and the Common Cold (24). I feel that each of them was worthwhile and that neither would have been easily replaced by a more technical book. The second book (24) was written because I had discovered in reading the medical literature that there was much evidence there about the value of ascorbic acid in decreasing both the incidence and the severity of the common cold and that this evidence had been suppressed or misrepresented by the medical and nutritional authorities. Since publication of the book, eight new studies have been reported. Every one of these has verified the value of ascorbic acid. The APA report shows the same sort of negative attitude as that shown by the authorities toward ascorbic acid in relation to the common cold. There seems to be a sort of professional inertia that hinders progress.

CONCLUSIONS

Orthomolecular psychiatry is the achievement and preservation of good mental health by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body, such as the vitamins. There is evidence that an increased intake of some vitamins, including ascorbic acid, niacin, pyridoxine, and cyanocobalamin, is useful in treating schizophrenia, and this treatment has a sound theoretical basis. The APA task force report Megavitamin and Orthomolecular Therapy in Psychiatry dis-
cuss & vitamins in a very limited way
(niacin only) and deals with only one or
two aspects of the theory. Its arguments
are in part faulty and its conclusions are
unjustified

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Dr. Pauling Comments on the Comments

Sir: I believe that the comments made by Drs. Wyatt, Klein, and Lipton on my paper "On the Orthomolecular Environment of the Mind: Orthomolecular Theory" (November 1974 issue) help to clarify the question, and I thank the three authors for their illuminating discussions.

In my article I concluded that the general condemnation of megavitamin and orthomolecular therapy by the APA Task Force on Vitamin Therapy in Psychiatry (1) is unjustified. Wyatt concluded that the principles of the orthomolecular hypothesis are reasonable and might be testable, but that there is no good scientific evidence as yet that megavitamin therapy is beneficial. Klein pointed out that society needs to know whether a treatment is effective or deleterious and that there is an unpleasant likelihood that orthomolecular methods will continue to be used in psychiatry without adequate scientific assessment. He mentioned his belief that only programmatic centers can develop the large-scale, adequate, and timely comparative factorial treatment studies necessary to answer the many complex questions in the field of psychiatric care. Lipton discussed some of my criticisms of the task force report. He mentioned the need for further evidence only incidentally, but I think that he would agree with Wyatt, Klein, and me that further studies should be made.

Much of Klein's comment dealt with the question of scientific inference. My conclusion, derived from the published studies, is that there is evidence (although it is far from overwhelming) that an increased intake of some vitamins, including ascorbic acid, niacin, pyridoxine, and cyanocobalamin, is useful in treating schizophrenia and that this treatment has a sound theoretical basis. In the task force report it is stated that the massive use of niacin "has proved to have no value when it is employed as the sole variable along with conventional treatments of schizophrenia" (1, p 46). One of my criticisms of the task force report is that this statement cannot be supported.

Klein stated that "one cannot prove a negative assertion, i.e., that a drug is no different from placebo." I gave the following brief discussion of the question:

A failure to reject with statistical significance the null hypothesis that the treatment and the placebo have equal value is not proof that the treatment has no value. The explicit statistical analysis of an alternative hypothesis should be carried out: for example, the hypothesis that there is a 10-percent or 20-percent greater improvement in the treated subjects than in the placebo subjects. No such analysis has been published.

My statement was so brief that Dr. Klein misunderstood it. His discussion of this point began as follows:

Insofar as I understand his exposition, Pauling seems to be saying the following: Consider an experiment that finds that a drug is 30 percent more effective than placebo in the samples studied, but that the 30-percent difference could easily have arisen from sampling fluctuations. One has no way of telling this 30-percent sample difference from a true zero-percent population difference. Therefore, the null hypothesis of no difference in the sample populations cannot be invalidated. Pauling says one should also make a test against the possibility that there is a true 10-percent or a true 20-percent population difference.

That is not what I said. Let us consider a study in which niacin is given to a sample of 20 subjects taken at random from a given population and placebo is given to a sample of 20 from the same population. Let us assume that 10 subjects in each sample improve The
conclusion might be drawn that niacin has no greater value than placebo. It is on the basis of studies such as this hypothetical one that the task force reported that niacin has proved to have no value. My question was whether a study such as this has shown, at a certain level of confidence (e.g., the customary 95-percent level), that there was less than 10-percent or less than 20-percent greater improvement in the niacin sample than in the placebo sample.

Reference to statistical tables shows that, because of possible sampling errors, this hypothetical experiment does not eliminate at the 95-percent confidence level the hypothesis that, relative to placebo, niacin increases by as much as 50 percent the fraction of subjects who improve. If niacin and placebo were in fact equivalent, studies of much larger samples would be needed before it could be proved with statistical significance that niacin has little value. As I pointed out, no such analysis has been made to justify the statement made by the task force about niacin I have not made a thorough statistical analysis of the niacin studies that are described as giving negative results, but the rough calculations that I have made indicate that they do not reject at the 95-percent confidence level an effectiveness of niacin as great as that claimed by the proponents of megavitamin therapy.

Klein wrote that "one further problem is Pauling's incomprehensible acceptance of very minimum differences that lack statistical significance as solid evidence of therapeutic efficacy." I feel that this remark distorts the facts I have said that there is evidence that megavitamin therapy has value. It is not necessary that the results of a study be significant at the customary level of p < 0.05 (which is quite arbitrary) in order to constitute evidence. There are recognized methods for combining the results of several independent but similar studies with low statistical significance into a result with higher statistical significance. I have criticized the task force for making strong statements that are not supported by the evidence. I do not think that my paper contains any incorrect or unduly strong statements.

In this connection, Klein stated that he was baffled by my having appraised a study (2) which both he and I consider to be a poor one that contains methodological errors. A main reason for my inclusion of this study was that one of its authors was a member of the task force. Another reason for mentioning it was that it is pertinent to orthomolecular therapy in psychiatry but was not mentioned in the task force report. It was a double-blind study and deserved to be mentioned both in the task force report and in my article.

I pointed out that derivatives of pyridoxine are known to be coenzymes for over 50 enzymes and that the chance of a genotype with need for a large intake of the vitamin is accordingly great. I also stated that there is evidence that pyridoxine is involved in tryptophan–niacin metabolism. I described the study (2) and quoted the statements made by the investigators about their results as well as a comment by Hawkins. I did not appraise the study myself; Klein errs in saying that I did. I quoted the statement, "On balance, these results suggest that the addition of pyridoxine may potentiate the action of nicotinic acid. Thus pyridoxine seems to be a useful adjunct to nicotinic acid therapy" (2), which was made in an article that was coauthored by a member of the task force but was omitted from the task force report.

Both Klein and Wyatt discussed my reference to the work of Greenbaum (3), who reported no statistically significant differences in a double-blind study of schizophrenic children receiving niacinamide or placebo. Klein stated that I pointed out that the children given niacinamide showed greater positive gains on a critical scale than the control subjects, although not at a significant level. He also pointed out my statement that the study "indicates that niacinamide has greater value than the placebo, even though it fails to show this at the customary level of statistical
significance. Klein responded to this with the following statement:

This seems utterly incorrect. The mere fact that one sample had a bigger effect than another sample does not justify the statement that "niacinamide has greater value than placebo," since this is a statement that generalizes to the population relationship.

Klein is wrong in suggesting that my statement or argument is incorrect, although of course it may have seemed utterly incorrect to him. First, I did not state that niacinamide has greater value than placebo; what I said was that the Greenbaum study indicated that niacinamide has greater value than placebo, even though it failed to show this at the customary level of statistical significance. Even if the study had indicated a greater value for niacinamide at the p < 0.05, p < 0.01, or p < 0.001 level, I could not have said simply that the study proved niacinamide has greater value. I could state only that it indicated this at a certain level of statistical significance. There is nothing holy about the 95-percent level of confidence. A study may provide evidence whether or not it reaches this conventional level.

Greenbaum's paper (3) permitted only a rough estimate to be made of the p value for this comparison of his niacinamide and placebo subjects. The value of 37 given by Wyatt (obtained from Greenbaum) corresponds to p < 0.18 by a one-tailed test. The value of p (one-tailed) is pertinent to the question of whether the samples showing higher scores for niacinamide than for placebo subjects correctly represent the population from which they were drawn or whether they represent a statistical fluctuation associated with the selection of the samples from the population. There is an 18-percent chance that such a fluctuation would occur; that is, according to this calculation, it is five times as likely that niacinamide would give better results than placebo in the whole population than that the two are equivalent. Greenbaum's observation, might simply be the result of a sampling error.

Both Wyatt and Klein criticized my statements about the ethical questions associated with experiments on human beings. I see no reason to change my opinion on this matter.
SECTION V—Hoffer and Osmond's Comments on R. J. Wyatt's Comment (1974) on L. Pauling's report:

On The Orthomolecular Environment of the Mind: Orthomolecular Theory
We wonder why Wyatt bothered to write his comments since they are merely opinions lifted holus bolus from the Task Force Report. Since he makes exactly the same errors it suggests he did not bother to read the original reports. His criticisms are these:

1. That H Osmond in a brief background paper on orthomolecular psychiatry did not reprint the massive data we have published in a large number of papers since 1957.
2. That we did not again repeat all this data in our suicide paper where we restricted it to show how orthomolecular treatment markedly decreased the suicide rate.
3. That we exaggerated the safety of vitamin B3. He referred to a report by Chinaglia that five out of 14 patients were taken off vitamin B3. He referred to the Ban-Lehmann studies showing the need for phenothiazines was apparently increased and to Wittenborn's pigment studies. Nowhere does he refer to the massive evidence available in the literature showing that vitamin B3 is much freer of toxic reactions than any tranquilizer. He does not refer to the huge coronary study where out of several thousand cardiovascular cases on nicotinic acid no cases of acanthosis nigricans were reported, nor that in no one else's series has such a large proportion of the series had these innocuous skin changes. He does not refer to Wittenborn's group who found no increased need for phenothiazines, thus refuting Ban and Lehmann.

Wyatt thinks the fact we have reported no further double blinds in 10 years is data against the efficacy of orthomolecular therapy. He is unaware that we (1961, 1963) have been very critical of double blinds from a theoretical and practical point of view. We made a carefully calculated decision not to do any more. If psychiatrists are going to disbelieve our four double blinds, why should they believe another hundred if we were disposed to present them?

His economic argument is totally fallacious since it is comprised of:
1. The number of visits to a psychiatrist which are required much less frequently with orthomolecular therapy;
2. Fewer admissions to hospitals;
3. Recovery to the point they are able to pay substantial income tax as lawyers, doctors, and so on.

We challenge Wyatt to show us a series of schizophrenics who have recovered to this degree on tranquilizers alone.

Wyatt reports that three studies on acute cases failed to show significant improvement with niacin or niacinamide. An examination of the three references showed the following. One of them was a paper by Meltzer et al., who used NAD (which is not the same as either niacin or niacinamide and which has different dose requirements). The second paper is a study by Ananth et al. on chronic patients only. In the title of this paper it is clearly shown that this was a study on chronic patients. The last reference is to a nonpublished report. In a brief communication by McGrath a large number of acute and chronic patients were treated with niacinamide only, but only one-third of this group were acute. Thus, on close examination of Wyatt's statement one finds that his statement "there are three studies (12, 16, 21) in which acute schizophrenics were given niacin or niacinamide" is totally wrong. He is also contradicted by a recent editorial in the Canadian Psychiatric Association Journal 20, 97-100, 1975.

Comment on D. F. Klein (1974)
We totally disagree with Klein's thrust which seems to be that only when the
scientific community has accepted an idea is it a useful fact He ignores the history of medicine which shows that a large number of very useful treatments currently acceptable were exposed to as much criticism for as long as is ortho-
molecular psychiatry There have been gaps of 40 years and more in medicine between a discovery and its application In addition, he presents no evidence the psychiatric and scientific establishment are the same Very few psychiatrists are scientists, nor do they claim to be so Very few bother to read original material, being content to read erroneous reviews such as the one produced by the APA Task Force committee

Since the first double-blind compari-
son experiments in psychiatry were conducted under our direction using a design which is still considered the way one does these experiments, we find it hard to understand how Klein can fail to accept conclusions from our first double blinds while accepting the so-called double blinds of Wittenborn and Ban and Lehmann The studies he favors were at best semi-blind, but it would be thoroughly dishonest to consider them double blind when patients were so easily identified by the flush

If Klein were motivated to use his position as Director of Research to repeat our work as described, i.e., similar patients, the same treatment, and the same method of evaluation, he would do much to settle the controversy Action, not good advice, is required

Comment on Lipton (1974)

Lipton's arguments are what one would expect from one of the most violent and bitter opponents of orthomolecular treatment His arguments are, as they have always been, irrelevant and trivial, especially his views on toxicity As clinicians who have used megadoses of vitamins since 1952, we are in a stronger position to judge their relative toxicity than Lipton who has not yet given any megavitamin treatment to patients Every year we are confronted with cases of jaundice, blood dyscrasias, tardive dyskinesia, thought blocking, and attempted suicide (many successful), sexual impotency, and a variety of neurological disorders in patients referred to us who have already been on tranquilizers for many years Every year we have to deal with intelligent patients immobilized by their constant tranquilizer medication, oral or parenteral, who are totally unproductive We would rather deal with the occasional case of nausea and vomiting, with the ubiquitous initial vasodilatation produced by nicotinic acid, with the occasional allergy to the tablets, and with the infrequent benign case of hyperpigmentation The undesirable side effects of vitamins are minor irritants and have never caused death The undesirable side effects of the phenothiazines and their toxic reactions would require a volume to report and to describe There can be no comparison between the undoubtedly toxic tranquilizers which the committee accepts as the best that modern psychiatry can offer for schizophrenia and the minor side effects of vitamins Perhaps this is why Lipton does not present any comparable data for toxicity as he does so frequently for efficacy

His concluding statement is mistaken. There is, on the contrary, increasing evidence that vitamin therapy now used over 20 years for some patients has not only not caused any harm to the patient, but has instead so sharply reduced the dose of tranquilizer required that even these toxic drugs can be used with safety The final result of many years of tranquilizer medication has been the production of the perfect human con-
sumer, of welfare, of nursing support, medical support, community psychiatry, and with no hope of ever being any better Has Lipton ever studied the fantastic costs to patient and community of perpetually chemically produced tranquility—of the perfect chemical straight jacket?
SECTION VI—Comments on the Double-Blind (Placebo) Methodology

We will summarize the ideas of those who are not enamoured with double-blind techniques as the only ones available to physicians. This we do to illustrate that there is a good deal of opposition toward accepting placebo experiments (all double-blind experiments must eventually begin with one containing a placebo) as the only valid method for judging the efficacy of treatment or of drugs. Since the committee accepted only experiments they considered to be double blind, even when they were not, these ideas summarized here provide an attack upon the committee's basic notion. It was this erroneous premise that permitted them to ignore a vast amount of clinical data corroborating orthomolecular therapy. The onus remains with them to present data proving that the double-blind experiment really is an effective method for sorting efficacious from noneffective treatments. We will begin with a few quotations from Claude Bernard, the pioneer in the development of clinical controlled experiments.


"It is therefore clear to all unprejudiced minds that medicine is turning toward the permanent scientific path. By the very nature of its evolutionary advance, it is little by little abandoning the region of systems, to assume a more and more analytic form and thus gradually to join in the method of investigation common to the experimental sciences."

"These men (talking about systematizers) start in fact from an idea which is based more or less on observation and which they regard as an absolute truth. They then reason logically and without experimenting and from deduction to deduction they succeed in building a system which is logical but which has no sort of scientific reality. Superficial persons often let themselves be dazzled by this appearance of logic; and discussions worthy of ancient scholasticism are thus sometimes renewed in our day."

"Men who have excessive faith in their theories or ideas are not only ill prepared for making discoveries but they also make very poor observations."

"But it happens further quite naturally that men who believe too firmly in their theories do not believe enough in the theories of others. So the dominant idea of these despisers of their fellows is to find other's theories faulty and to try to contradict them. The difficulty for science is the same. They make experiments only to destroy a theory, instead of to seek the truth. At the same time they make poor observations because they choose among the results of their experiments only what suits their object. By these two opposite roads men are thus led to the same result, that is, to falsify science and the facts."

"It is said that coincidence may play so large a part in causes of statistical errors that we should base conclusions only on large numbers. What a physician needs to know is whether his patient will recover and only the search for scientific determinism can lead to this knowledge. But when determinism increases, statistics can no longer grasp and confine it with a limit of variations. There we leave science for we are forced to invoke chance or an occult cause to regulate phenomena. I therefore refuse to acknowledge that science has a place for men who make criticism their specialty, as in letters and in the arts. To be really useful criticism in every science must be done by men of science themselves and by the most eminent masters."

"Pure contradiction would amount to an accusation of lying and we should..."
avoid it because happily scientific falsifiers are rare. As such cases moreover have no connection with science, I need not offer any precept on the subject I wish merely to point out here that science does not consist in proving that others are mistaken; it can be a profitable work for science only insofar as we show how he was mistaken.

"Physicians often pride themselves on curing all their patients with a remedy that they use. But the first thing to ask them is whether they have tried doing nothing, i.e., not treating other patients; for how can they otherwise know whether the remedy or nature cured them? From all this I conclude that comparative observation and experiment are the only solid foundation for experimental medicine."


"If there are problems—ethical, scientific and even mathematical—associated with controlled trials it nevertheless remains the case that this technique holds out greater promise for advance in therapy than any yet devised. More important, however, is it that recognition of the scientific basis upon which such trials are constituted will insure so far as is possible that the undesirable state of affairs prevailing in medicine during the first half of this century will never be repeated to the extent of producing so many false trails and so many unnecessary and unworthy modes of therapy."


"The Establishment in Canadian Medicine insists on the method of controls, especially what Gilder called 'one of the fetishes of experimental medicine' the double-blind clinical trial. Editors refuse new and promising work unless accompanied by an 'adequate series of normal controls,' except an occasional article from the right source, if in line with what is 'accepted' by the 'authorities.' One editor stated over his signature that 'case reports would not be considered as evidence.'

"An American when told about a new idea usually asks, 'What is it?' but the Canadian asks, 'Who is doing it?' However, one American editor said his magazine never reported clinical material not accompanied by suitable controls. Concerning a disease known to be always fatal within five years, would he not report 10 cases who lived 10 years with a certain treatment, but would publish five cases if the other five had been allowed to die in the accepted manner? Absurd, you say! Control-worshippers are a bit absurd! But there are signs of rebellion against their retarding progress any longer.

"In science a controlled experiment means every variable is held steady except that being studied. This is impossible in clinical medicine! In the average 'controlled' clinical observations are the following equally balanced? Nutrition, smoking, drinking, sexual or marital adjustments, pregnancy, previous medication or treatment, desensitization or immunization, differences in social classes (affecting precautions, exposures, cleanliness, natural vaccination from exposure, plumbing), blondness, or brunetteness, size, body build, mental type, inheritance, etc. How controlled is an experiment which assumes none of these affects the result?"

"The value of the so-called double-blind study is much questioned today by many thinking writers, who suggest the following: It is not a foolproof mechanical means of insuring a correct interpretation of result. It may mislead as well as lead. The objectivity of the double-blind study is a medical illusion. It is time that the double-blind approach be prevented from developing into a triple-blind disaster. The use of the double-blind technique does not guarantee the sanctity of the trial."

"The insistence in recent years on 'blindness' or 'double blindness' in evaluating the effect of therapy is an insult to the intelligence of the average clinician. Most new drugs today provide symptomatic relief and are not curative. The ultimate observation is made by the patient, who alone knows whether or not he is relieved of his subjective symptoms. Relief due to psychotherapy and suggestion is nonetheless relief.

"Use of a placebo is based on the assumption that the placebo has no effect or that its psychotherapeutic effect will equal that of the drug being tested. Neither assumption is necessarily true. In the Proceedings of the Royal Society of Medicine (The Placebo and the Clinical Trial, 57: 67, January, 1964) James Parkhouse points out that the physician himself cannot escape being a placebo to some extent: but that in any case, one of the first things to be realized, therefore, before embarking lightheartedly upon the use of a placebo is that far from clarifying the issue it may merely add confusion."


"The asylum clinician has such great advantages in regard to the observation of the action of these medicaments that it is a neglect of opportunity if he fails to lead and instruct the whole medical profession in this respect. In private or out-patient practice, and even in ordinary hospitals and sanatoria, the results of any mode of treatment are liable to be vitiated by variations of diets and habits of life, which are entirely beyond the ken of the physician. In the hospital for the insane, on the contrary, the diet and habits are under almost absolute control, and observation on the results of treatment should be much more reliable."

"Bigelow considers the administration of placebos in the clinical evaluation of psychotropic drugs in a number of instances a source of error. He argues that unless the placebo is administered in such a fashion that an observed emergent can be clearly linked either to the placebo, the test substance, or both, then obviously administration of the placebo has been fruitless and any consideration of the validity of the given result merely because placebo was given is unwarranted. Moreover, he claims another pitfall arises from the necessity that the placebo itself has to be rigidly controlled. If orally given it must have physical characteristics analogous to the active medication and it has to be administered in the same fashion with identical procedures as the real drug.

"From a theoretical point of view, in human beings where transaction of processes is present, a double-blind controlled study seems to be essential to eliminate the bias that might be introduced through feedback mechanisms between the observed and the observer. (11) However, in Batterman and Grossman's experiment the double-blind method for some unknown reason obscured the presence of an actually existing pharmacotherapeutic property of the drug which arose when they switched to a single-blind placebo trial. Furthermore in Uhlenhuth's experiment the therapist's attitude broke through the double-blind experiment and Hoffer and Osmond (8) argue that the double-blind method, when the group under study is not homogeneous, may obscure the presence of significant differences.

"It is really unfortunate that the statistical method also has its own pitfalls. (5) Some of these were expressed by Huntsman by the following: 'The prestige of mathematics is so great that many persons forget that even in mathematical hands, probability, chance and random mean ignorance. They come to think that in the alembic of mathematics chance in some way becomes certainty. They take great care to select random samples without realizing that insofar as a sample has been random, they don't know how it..."
was selected (9) A more severe criticism was launched in the Lancet by Wiener quite recently (1962) (14) According to him, many clinical investigators 'because they are unduly sensitive or insecure regarding their lack of mathematical training and knowledge habitually hand over all their data to biometricians for analysis in order that their papers may include the appropriate tests, standard errors and so on In that way they have come to depend more and more on mathematicians who have no knowledge or understanding of the subject to interpret their findings, instead of relying on their own experiences and common sense ' Wiener concludes that mathematics is a poor substitute for accurate observations, reliable experimentation, and common sense "


"There has long been abroad in the land of clinical research the notion that comparisons between groups of patients is the sine qua non of statistically valid scientific clinical research, and that the study of the individual case must be relegated at best to a status of intuition and the clinical hunch, not capable of statistical testing and validation For reasons that have been discussed in some detail (5, 6) this view is seen to lack validity in its own right It has unfortunately tended to perpetuate a basically superficial methodology as a unique prototype for science in clinical research with mental patients "


"In double-blind evaluations of drugs neither the patient nor the physician can know what is being administered; such studies are also called controlled when the patients are randomly assigned to a placebo and a drug-receiving group. The protocol is formulated at the beginning of the study and must be followed meticulously to the end It would obviously be absurd if these types of studies should become the law of the land "


"After generations of doctors have accepted without question the opinion of the great names in medicine, a change has come about so that little or no credence is now given to clinical observations even by experienced investigators. This change in official attitude is probably a step in the right direction, but one wonders whether the pendulum has not swung a little too far, allowing a blind acceptance of double-blind trials without a critical evaluation of their shortcomings and their ability to mislead as well as to lead "

Dinnerstein, A. J., Lowenthal, M., and Blitz, B. The Interaction of Drugs with Placebo in the Control of Pain and Anxiety, Perspectives in Biology and Medicine, 10, 103-117, 1966.

"For scientists attempting to understand the action of analgesic and psychoactive drugs, it is suggested that the simple double-blind study is not an adequate experimental design. A given drug may produce opposite directions of effect on pain or anxiety in different emotional and instructional contexts. It may produce opposite directions of effect in different subjects within the same objective context. The simple double-blind study, employing a single set of instructions and subjects treated as a random variable, is thus inadequate in that it provides no hint concerning the degree to which the observed drug effect is dependent on contextual, instructional, and subject variables."


"My purpose in this essay is to show
that our act of faith is a delusion. The methods do not exist. There are no satisfactory standard procedures for assessing the safety and efficacy of drugs. Despite general acceptance, the existing techniques are oversimplified, naive, and grossly inadequate for the needs of clinical medicine.

"These intellectual maladies of clinical therapy cannot be cured merely by the further application of inappropriate statistical theories, by 'crash' programs and bureaucratic fiat, or by recommendations from scientists who have had little or no personal responsibility for the continuing care of patients. The problems arise in clinical activities, and can be best perceived and solved by connoisseurs of those activities.

"The public will continue to demand regulations that assure the safety and efficacy of pharmaceutical therapy and regulations will inevitably be created in response to this demand. Without modification of current procedures, however, the regulations will succeed in replacing 'clinical experience' that is scientifically unspecified by 'scientific' statistics that are clinically worthless. If academic and practicing clinicians want these regulations to be both scientifically meaningful and clinically sensible, the clinicians cannot continue to evade their own paramount responsibilities while complaining about the work done by the statisticians, pharmaceutical companies, and federal personnel to whom the responsibilities have become allocated by default."


"These principles of biometric science have proved suitable for the experimental goals and data encountered with the animals or agricultural crops for which they were developed. However, they do not deal with scientific problems in selecting the type of information that is to be appraised in the therapy of sick people. In particular, biometric methods do not contain provision for evaluating the complex, crucial data that distinguish a person from a dog or a field of wheat.

"The treatment of patients requires attention to at least three issues that become paramount in experiments where the 'material' is a person: (1) of the many things that can happen when a person is treated, which will be chosen as the indexes of accomplishment; (2) from the many changes observed in these indexes, how do we rate each change for its desirability as good or bad; (3) how do we combine these multiple individual ratings of desirability into a single rating that represents the final decision? The controlled, statistical randomised procedures do not currently provide data to answer these questions.

"There are many scientists in academic or government advisory positions today who seem to prefer a 5 percent improvement rate which seems scientifically 'pure' to a scientifically 'impure' rate of 68 percent.

"Fortunately, of course, aspirin had been used for decades before development of our current scientific doctrines. Millions of people already knew about aspirin's many benefits and recognised its hazards as relatively infrequent and slight. Aspirin has been appraised and deemed beneficial by an empiric but balanced scheme of assessment that is sometimes called 'common sense.' Aspirin might never be approved if subjected to the unbalanced assessments used in modern therapeutic science.

"A different problem in balance relates to evaluations performed by experts usually chosen from the ranks of academic scientists and clinicians working full-time at a university or other research institute. An academician seldom sees the patient or the patient's family at home, and seldom follows a patient for an extended period. The total picture of human therapy—with all its effects on performance, convenience, anticipation, family, and economics—will not be regularly seen by an academic specialist.

"The evaluation of all the humanistic data associated with therapy will there-
fore require additional judgments from sources outside the academic or government enclaves. These sources will include full-time practising doctors, patients, and others who are familiar with the total picture. These 'consultants' may not be connoisseurs of current doctrines in science, and may not speak the magisterial language of statistics, but they can often provide experience, wisdom, and common sense in a situation for which contemporary science is inadequate. This type of consultative judgment will be especially necessary in evaluating over-the-counter medications in which doctors do not participate and for which all of the anticipation effects occur in the patient.

"Until the methods of science are made satisfactory for all the important distinctions of human phenomena, our best approach to many problems in therapy will be to rely on the judgments of thoughtful people who are familiar with the total realities of human ailments. Human testimony and human judgments are not objective; they may not be precise; and they are often fallible. At this stage in the development of human science, however, our primary challenge is to assemble information that is meaningfully human, even if scientifically imperfect. We shall advance the progress of neither science nor humanity by obsequious adherence to scientific doctrines that provide quantitative glitter and 'statistical significance', while de-humanising our data, confusing our sensibility, and diverting our attention from the people who are the only proper subjects for the study of mankind."


"Those studies which included within their structure the double-blind, placebo-controlled technique showed significantly lower clinical improvement rates than those which did not."

"Long-term studies showed significantly higher clinical improvement rates than did short-term studies, demonstrating that duration of therapy, as well as degree of 'blindness', may be a very meaningful variable in determining clinical outcome."

"Duration of therapy was significantly related to degree of 'blindness' in that only one of 11 double-blind studies was long term and only four of 16 single-blind studies were short term."

"Long-term, single-blind studies showed appreciably higher clinical improvement rates than did short-term, double-blind studies. The very meager number of long-term, double-blind studies (1 only) and, to a lesser extent, of short-term single-blind studies prevented us from differentiating between degree of 'blindness' and duration of therapy regarding their relative impact on improvement rates. Thus, no clear-cut certain evidence could be adduced either to support or nullify the contention that the double-blind, placebo-controlled method is, per se, a necessity for the 'accurate' clinical evaluation of a drug.

"We were unable to demonstrate a general decline in improvement rates with the passage of time. Thus we could not validate the commonly held belief of a progression from an initial over-enthusiasm to a later realism in the subjective evaluation of a drug."


"A third general area is the worship of the controlled trial. Having spent a lot of time in my life arguing on behalf of the controlled trial, I think I know its values as well as its limitations. I am sorry that so many people have overbought the concept of the controlled trial and that other valid ways of acquiring evidence have been neglected. L-dopa is an example of how a drug can be rated as ineffective on the basis of poor double-blind controlled trials, several of which were done early in its history. Because inadequate dosages were used for in-
adequate periods of time, there was no significant effect. It was on the basis of uncontrolled trials of L-dopa (as well as on all the beautiful logic and experimental data that preceded it) that one came to the conclusions, and rightly so, that this drug was a dramatic therapeutic advance. We have only to remind ourselves that all sorts of highly important psychoactive agents such as barbiturates, meprobamate, chlorpromazine, imipramine, etc., were discovered by ways other than the formally controlled trial.


"(a) 'Anecdotal' or 'uncontrolled' observations. Usually these phrases are used in a pejorative sense, despite the fact that such observations constitute the oldest method for studying drug actions and remain a mainstay even today. The point too readily forgotten is that they are in fact not 'uncontrolled.' The control consists of what the observer believes would have occurred in the absence of the drug.

"(d) The comparative randomized trial. This approach is relatively new. The so-called trial in the Book of Daniel in the Bible or the famous trial by James Lind on H. M.S Salisbury on citrus fruits and scurvy are really not modern trials in the strict sense! For example, Lind's experiment would be criticized today because of a difference in baseline variables in his therapeutic groups. He took two patients very sick with scurvy and purposely assigned them to the citrus fruit diet, which he suspected would be beneficial. The therapeutic results were dramatic, but the supersceptic could have accused him of using a population that was destined to improve because they had nowhere to go but up! (They could have chosen to die, of course, but such trivial points have been known to be completely ignored by a supersceptic with blood in his eye.)

"There are many ways in which controlled trials can go wrong. One can come to the conclusion that no difference exists between treatments because the population has been chosen in the wrong way, because the numbers are too small, because the observations were too sloppy, or because the patients failed to take their medication. If a new drug has been compared against placebo, one may erroneously conclude that the drug is ineffectual, since the errors suggested above will tend to 'prove' the null hypothesis.

"(h) Professional judgment and the marketplace. Popularity among the public or among physicians is not tantamount to worth. On the other hand, there are interesting examples of drugs that have sold well despite an absence of advertising, or compounds that have failed despite a good deal of advertising, and suggest that the physician or the patient is not completely devoid of discriminatory ability. It is generally assumed that expert 'anecdotal' judgments are better than non-expert 'anecdotal' judgments, despite the fact that there are some compelling instances where the practising doctor has discovered truths that the experts failed to recognize.

"Schneller has recently suggested that experts in the science of clinical investigation are not the same as experts in the art and science of treating patients. He states: 'For the one kind of expert to dominate the drug usage of the other is like a Sebring race driver setting the operating regulations for New York City taxicab drivers.'

"It is my contention that three or four well-done trials by people who are expert in a field, with conclusions that are similar, is enough to demonstrate that a drug has effectiveness. The accumulation of thousands of patients often serves, I believe, merely to provide psychological comfort.

"Weiner has suggested that for drugs used for a long time with apparent success and without evidence of significant toxicity, the burden of proof should be on those who claim that such drugs do not work.

"It is quite possible that the new
developments in regard to 'substantial evidence' are carrying us farther and farther away from the real-life situations in which drugs are ultimately to be applied. Certainly most drugs are not given under the circumstances of double-blind technique, obtaining informed consent, hospitalization, the avoidance of other simultaneous therapies, the application of drugs by experts, etc.


"This double-blind method has been criticized on several grounds. First, in many cases drugs produce side effects which are easily noticed by the evaluating psychiatrist. These effects immediately eliminate his blind condition and enable his expectations to begin to affect his judgment. Since differential side effects are an almost universal concomitant of any therapeutically efficacious drug, it is practically impossible to keep an observant psychiatrist really blind to the medication being used.

"A second argument against the double-blind technique is that it creates a highly artificial situation which has little relevance to the clinical setting in which any drug would actually be used. The cold, impersonal evaluation of changes is not typical of clinical contact. In the language of stimulus sampling theory, such evaluation has little 'ecological validity.'"

Clearly there is a growing recognition that the double-blind technology is only one of a number of methods for testing drugs and that it has so many errors and biases that it ought to be used sparingly and with scepticism. It will never replace clinical judgment although it may continue to serve to allay the anxiety of editors and government officials who need reassurance their decisions will not be criticized in the future. The double-blind technique is most cherished by those professional people who have the least contact with patients. It is rare to find clinicians who enjoy doing double-blinds, believe the results of double-blinds published by others, or defend them in any public debate.

It is unlikely that double-blind experiments really are double-blind for even what appears to be a simple task of preparing placebo tablets, similar in every respect to tablets containing the active medication, may be extraordinarily difficult. Joyce (1968) remarked that in none of the 20 clinical trials he had been involved in had the first attempts of the manufacturer at identical formulation been successful. Hill et al. (1976) studied 22 pairs of agents used in published double-blind controlled experiments. A panel of four observers found only five pairs so closely matched they were indistinguishable, but in seven pairs all four observers detected obvious differences. This is not very encouraging, but even worse is the fact that the medication may cause changes in the person which are easily distinguishable. Some agents discolor the urine (rifampin or riboflavin), stain the linen (p-aminosalicylic acid), or produce physiological reactions such as the flush (vasodilation) of nicotinic acid.

Hill et al concluded, "It may be very difficult to produce indistinguishable preparations for use in 'double-blind' trials and that as a consequence such studies are often not double-blind at all. They add, "The facts that stand out are that, unless the organization of the study is appropriate, the interpretation of the results may remain in doubt and that the 'double-blind' study is an idol which may and often does have feet of clay."

We have presented our views in several published papers. Our conclusions arose from our experience with double-blind experiments which we began in 1952, long before most psychiatrists had the slightest idea what the method was. We have not been able to find any double-blind study in psychiatry which preceded
ours Dr. A Shapiro in his extensive search of the placebo literature has not been able to find any one either, at least he has not been able to support by any reference to the literature his thoughtless statement made in a letter to JAMA that we were not the first. We are still waiting for his statement admitting his error which he seems reluctant to make.


The reader should note that our papers were written and published long before the APA Task Force Report on megavitamin therapy was published. It does not appear that in their inadequate examination of the megavitamin literature they recognized the importance of our objection to the methodology by which they came to set such store. However, we need not be surprised by this omission for as we have noted here, Dr. Thomas Ban, one of the Task Force members, apparently shares our scepticism when not engaged in his Task Force duties.

A Theoretical Examination of Double-Blind Design

A Hoffer, MD, Ph.D., F.A.P.A., CRCP, [C],
Saskatoon, Sask.

Recently an eminent surgeon wrote that A Bradford Hill's contribution to the design of controlled experiments was equivalent to Fleming's discovery of penicillin. This statement by a surgeon, who freely admitted that the double-blind method had no place in surgical research, indicates how convinced some physicians are that this method will prevent serious errors in the development of new treatments, and will lead us to new heights in therapeutic discovery. According to Atkins, every therapeutic discovery made before 1945 was made by researchers of Nobel calibre such as Lind, who discovered that oranges and lemons could cure scurvy. Since we have double-blinds, we need no longer depend upon these sporadic occurrences of geniuses to discover even better therapies. We need no longer breed Harveys, Pasteurs, Ehrlichs and Flemings.

I wish I could agree with this optimistic view. It is my thesis that controlled experiments are not new, that they go back certainly to Lind, that our Nobel laureate colleagues have always used controlled experiments, that the only thing new is the "double-blind", and that this double-blind addition has created so many new difficulties and errors that it should be re-examined carefully and rigorously.

A surprising number of younger scientists are convinced that controlled experiments are new in medicine. This may be a reflection of our ignorance of medical history and the rapid adoption by governments, grants and editorial committees of the false idea that only double-blind clinical experiments are controlled experiments. A double-blind experiment is one in which neither the people evaluating the results of treatment nor the subjects being evaluated know whether they have been given an inert substance or a substance shown in previous pilot experiments to be active. One may compare two active substances, but, in the end, reference must be made to the placebo for base-line activity.

To equate double-blinds with a controlled experiment leads many to assume that once an experiment is "blinded" no other controls are required. It is more accurate to talk about comparison...
experiments since one treatment is compared to another. Comparison experiments may be open, single-blind, double-blind, or if you like, multiple-blind.

Comparisons between treatments have been made by physicians for centuries. The history of discovery in medicine is the history of trial and error, and recognition of error indicates that comparisons have been made. A controlled experiment was reported by Pare in the seventeenth century when he compared the effect of crushed onions on burns by applying them to only half the body. Lind in 1747 compared the effect of two oranges and one lemon per day on two scorbutic patients against the effect of standard treatment in 10 cases. Only the two recovered. Claude Bernard frequently discussed the need for controlled experiments and, of course, men like Pasteur and Ehrlich performed only comparison experiments. Claude Bernard pointed out that a comparison group (his word) should provide an estimate of the natural remission rate. Any treatment must do better than this if it is to have any value in medicine.

Theoretically the double-blind method is designed to test the efficacy of a drug free of the influence of bias in the observer and faith in the patient. It is assumed that bias and faith confound the results of other kinds of comparison experiments.

Since, as far as I know, no experiments have been recorded which prove or suggest that the double-blind does compensate for these variables, it is possible to examine it only theoretically, as we are in the presence of a standard clinical method which has never been calibrated or subjected to the hard test of experiment. Since what were probably the first two double-blind experiments in psychiatry were conducted under my direction, we have had nearly 14 years of continuous experience with it. I am, therefore, to some degree responsible for the present popularity of the double-blind method.

There are several theoretical objections to the use of the double-blind. There are, of course, ethical and practical difficulties as well.

1. Role of Probability Theory
   Probability theory was invoked as a way not only of randomizing groups, but of determining the significance of a finding; that is, a statistical test was made to see if the results observed could have by chance occurred with an inactive drug. But no clinical trial satisfies two of the basic theorems upon which probability theory is based. This matter was recently discussed by Hogben. Probability theory was developed partly as an aid to English noblemen, who wished to win at the gaming tables in Monte Carlo. According to Hogben, a calculus of probability is relevant to the real world (a) only in so far as it specifies frequencies of observable occurrences in an indefinitely protracted sequence of trials, (b) only if also such occurrences collect a sequence wholly devoid of order. Neither one of these essential conditions is present in clinical trials. When one gambles with dice, it is possible to use dice manufactured to precise standards. One can assume that a man one thousand years from today who throws these dice by carefully prescribed techniques will come up with the same probabilities, i.e., the dice have been made invariant; but every biological phenomenon is subject to minor and major cyclical changes. Since human observation beyond one life span is difficult, it is hard to measure changes over decades or centuries, but it is pretty clear we do not live in the same world as did our grandparents. Biological phenomena are subject to remarkable evolutionary and geophysical drifts. It is, therefore, possible to specify phenomena rigorously, but not to ensure an indefinitely protracted sequence of trials. Nor are our sequences wholly devoid of order. Perhaps these considerations worried Sir Ronald Fisher, because, before his death, he expressed to his students great concern about the direction clinical trials were taking.

   One of the assumptions in probability theory is that the population from which
the sample is drawn is homogeneous. But in psychiatry, where diagnosis is highly subjective and, therefore, imprecise, it is impossible to have homogeneous groups. Double-blind studies have been reported using antidepressants for treating depression. The matched groups contained endogenous depressions, schizophrenics who were depressed and neurotic depressives. When heterogeneous groups are used, the therapeutic response is so variable that the response of the treated and control group depends too much on the random distribution of different classes of patients in them. No provision is made for this in the double-blind controlled design.

2. Control of Bias

It has been assumed that not knowing whether a patient is receiving drug or placebo will reduce or eliminate bias. If the code remains unbroken and the experiment remains truly blind, this is probably true. But the double-blind introduces serious new biases of its own, which may be even more misleading.

There are at least three major variables in any therapeutic program. The first is that feeling of trust or faith the patient has in his doctor and, therefore, in his therapy. The second factor is the faith or confidence the physician has in himself and in the line of therapy he proposes to use. The third factor is the therapy. The best results are obtained when all three variables are set at their optimum level. If he has little faith in the doctor, the patient may or may not follow the recommended treatment. This may explain why a large proportion of patients tear up the prescription very soon after they leave the doctor's office. The patient's faith must sustain him until the treatment begins to work. It can be extraordinarily great. I know several patients whose faith in their doctors remains intact even after 10 years of therapy with no improvement.

The doctor's faith in his medication must also be maximum. This does not mean that he need be deluded about the response to therapy. The doctor with faith will encourage his patient to persevere, he will hold out the promise of recovery or improvement, he will minimize nontoxic side effects, he will not produce many iatrogenic side effects and he will remain interested and enthusiastic. If he has no faith in a medication he will be more apt to discourage the patient, to use improper dosage schedules, to maximize side effects and to discontinue treatment too early. Both these forms of faith, positive or negative, influence the therapeutic result, but since in office practice physicians do not use therapies of which they disapprove, the negative factors are seldom operative.

The double-blind technique makes it difficult to sustain these two variables at their optimum level. It is hardly likely that a doctor will have as much faith in a new drug as he does in drugs with which he is familiar, and when he is forced to work in a double-blind way his faith and enthusiasm are reduced to a very low level. It has been our tradition for centuries to abhor the use of placebo or trickery. For centuries doctors have condemned quacks. In the Middle Ages the only difference between quacks and doctors was that while the doctors were more honest, the quacks were more intelligent. Quacks knew their remedies were no good and so sold atmosphere, displays, catharsis and other trappings of nonmedical faith. Doctors used similar remedies which were no more therapeutic, but they had faith in their efficacy. In the end the doctors won because therapies in which we can justly have great faith developed.

Serious ethical problems are raised by double-blind techniques which further reduce faith. If severe toxicities should develop, one may have to break the code (and ruin the experiment) or run the grave risk of harming the patient. Conversely, in order to ensure that side effects are not missed, the physician may search for side effects in all his subjects too diligently and markedly increase iatrogenic side effects.

If the doctor is unenthusiastic about
the therapy, it is certain the patient will know it and his faith and enthusiasm will be dampened. Thus, two of the basic ingredients of the therapeutic process are set at very low levels.

There are undoubtedly drugs which in their natural setting, i.e., combined with optimum faith and hope, are very good, but which without these human factors are nearly inert. The double-blind is bound to destroy these compounds and so deprive us of valuable safe medica-
tions. To survive these serious limitations of the double-blind, the drug must be powerful and nonspecific. It may be said that the double-blind works best for compounds where it is least needed, e.g., for penicillin or nicotinic acid for pellagra.

When a biochemist wishes to test the rate of reaction of an enzyme which has an optimum temperature of 37°C, he will not get very far by putting his reacting vessel in a deep freeze. By running a double-blind we are, in effect, placing the therapeutic process in a deep freeze.

To confound double-blinds even more, it is doubtful if more than a small proportion of these experiments are really blind. Hardly ever does the design of the study ensure that at no time will the code be broken by doctor or nurse observers. In many psychiatric wards there is a tradition among nurses which ensures that every attempt will be made to break the code. Nurses are no worse than doctors and, like doctors, they also have ethical problems about giving their patients a placebo. They will chew, taste, swallow the tablets, suspend them in water, pound them with a hammer, throw them against the wall and stamp on them. They will study the fluid characteristics of the coded liquid in syringes and see how it mixes with blood which may flow back into the barrel. It seems the double-blind not only reduces faith to an undesirable low level, but brings out petty larceny in all of us.

An example of severe bias in medical reporting was recently described by Vogel et al.10 In 1960, Astin and Rossi reviewed the literature on the effect of glutamic acid on intellectual performance. These authors were so convinced that only double-blinds should be used that in their survey they ignored 25 clinical studies. By their selection of papers they were able to prove that positive results were obtained with clinical non-blind studies, whereas controlled studies usually showed glutamic acid to be inert. In fact, when all studies were included and errors in reading the original papers were corrected, it turned out that both non-blind and blind studies yielded similar positive results.

Do Double-Blinds Establish Good Therapies and Destroy Bad Ones?

If Atkins2 is correct, our present era of double-blind methodology should be characterized by a substantial increase in good (i.e., effective) therapies and by a massive reduction in poor or ineffective treatments. Perhaps this is true in some of the other branches of medicine, but unfortunately it seems not to have happened in psychiatry. Apparently the double-blind has not replaced our need for the Pasteurs, Bantings, and Flemings.

Not only should our era be remarkably successful in developing new therapies, but one should be able to ascribe these changes to the double-blind method.

### TABLE 1

The Relationship of Clinical Trials and the Introduction of New Therapies into Psychiatry

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Double-blind</th>
<th>Not blind</th>
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<tbody>
<tr>
<td>Acceptable</td>
<td>Tranquilizers</td>
<td>Anti-tension agents</td>
</tr>
<tr>
<td>Nicotinic acid for schizophenia</td>
<td>Modified ECT</td>
<td></td>
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<tr>
<td>Nicotinic acid for the psychosis of pellagra</td>
<td></td>
<td></td>
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<tr>
<td>Not acceptable</td>
<td>Mega-nicotinic acid for</td>
<td>Mega-thyroid for</td>
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<td>schizophrenia</td>
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have listed in Table 1 the treatments most frequently used in psychiatry. It would be useful if specialists in other branches of medicine would perform a similar exercise.

Not all new therapy in psychiatry has been developed as a result of double-blind methodology. On the other hand, we have a large number of very effective treatments including tranquilizers, antitension chemicals, antidepressant drugs, modified electroconvulsive therapy (ECT), penicillin for general paresis of the insane (GPI) and nicotinic acid for eradicating pellagra psychosis.

Chlorpromazine, first introduced by Delay and Deniker, was found by Lehmann and Hanrahan to reduce markedly psychomotor excitement. The hundreds of double-blind studies on chlorpromazine have added hardly anything to our knowledge of chlorpromazine. In fact, only a couple of years ago nearly one million dollars was spent in a well-designed double-blind study which suggested that chlorpromazine was a bit more active in controlling overactivity than starch. This study was appropriately reported as "the million-dollar fizzle."

Reserpine was introduced into American psychiatry about the same time Kline in the first study showed that it improved 22 percent of 200 patients with chronic psychosis to the point where they could be discharged. It was subsequently found that 86 percent were improved. At this point it may be useful to lay at rest another myth about clinical testing. It has become a cliche in psychiatry that any new tranquilizer must be used very quickly because with time the real value of the drug will have been proved to be nil, i.e., the initial flush of enthusiasm will have waned. If true, a drug company could become wealthy by simply putting out a new placebo with a name every year backed by enthusiasm-creating factors. Apparently drug companies have not considered this method. This myth was examined by Glick and Margolis, who reported that it was false. They examined reported recovery rates of the same drug over a five-year period and found no evidence of a decline in therapeutic efficacy.

Therapies replace each other if there are real advantages, one over the other. Thus insulin coma therapy was replaced by tranquilizers because tranquilizers worked more quickly, were cheaper and required less skill in their administration. It is still debatable whether the long-term effects are any better, and I suspect that the use of insulin coma may well come back. Similarly, chlorpromazine displaced reserpine. The rule is not that drugs are forsaken because they lose their efficacy, but that they are replaced by other more effective or less toxic therapies.

Two good therapies for schizophrenia were developed by double-blind technique which are not yet accepted. One is nicotinic acid therapy that we have been using since 1952. We have completed three double-blind controlled studies with follow-ups going back 14 years. Our 10-year cure rate is 75 percent compared to our comparison control rate of 35 percent. The other is high-dose thyroid therapy developed by Danziger and Lochner, Scheving and Flach. Finally, there is one good therapy for alcoholism, LSD, which will never be double-blinded.

All the "poor" therapies were developed by non-blind studies, but are acceptable to most psychiatrists. Thus it is clear that therapies in psychiatry have been developed by clinical studies and have received little help from double-blind studies. Non-blind studies have developed treatment methods which are poor, i.e., can be improved, but they have also given us excellent therapies which have revolutionized the treatment of psychiatric patients.
not led to the development of a single useful psychiatric therapy, and even when this method has been used as with nicotinic acid, the results have not been accepted.

Double-blinds are considered essential for clinical testing for many reasons. First, we have been confronted with a large number of new treatments and naturally it is important to know which ones are best for certain classes of patients. The clinical trials common before 1945 did lead to many polemics between originators and their detractors. It appeared to many scientists, especially those having no responsibility for treating patients, that the double-blind would settle these issues. Over and over I have observed that the most enthusiastic supporters of double-blinds are some statisticians, psychologists and others who never have done, nor will do, clinical experiments themselves, and physicians like deans and chairmen who order their junior men to perform them. Uniformly the physicians who are responsible for evaluation and treatment are much less enthusiastic about the method.

A second reason is that men given the responsibility of receiving and vetting research grants believed that this method or design would help in deciding who should receive a grant. The National Health Grant application forms all contained a question concerning the statistical design to be used. It soon became clear that no one could hope to receive a grant unless the double-blind method was described. Whether it was eventually used is a different matter. In any event, research workers are intelligent and easily conditioned, especially when the carrot of grant support is dangling before them.

When the work was done, journals refused to accept papers unless they described double-blind experiments, and soon the journals blossomed forth with self-congratulatory titles such as "a controlled study of Drug X," etc. And finally, drug houses discovered that when government agencies wanted data they wanted only a certain kind of data—i.e., double-blind data. In fact, many drug companies are now deluded into thinking double-blinds are not so bad after all; but then they do not have to run them. They merely have to find others who will.

A beautiful example of circular logic was used to bolster the double-blind technique. It is common knowledge that drugs, said to be effective when tested single-blind, turned out to be no better than placebo when double-blinded. It was, therefore, assumed that since the double-blind was infallible this proved that these chemicals really were inactive. It seems not to have occurred to these workers that since the double-blind had not been validated, or calibrated, it might be a dud method. In other words, one could just as logically assume that any method which could not demonstrate efficacy in drugs known to be active must be of little value.

This view was supported by Glick and Margolis, who discovered that double-blind experiments are of short duration, while single-blind experiments are of long duration. The double-blind is so difficult to operate that it must be a short-term experiment. If it ran for a long time, all the difficulties would be greatly increased. Since most psychiatric illnesses are chronic, it seems inappropriate to run short-term experiments.

In 1865 Claude Bernard wrote, "These men [talking about systematizers] start, in fact, from an idea which is based more or less on observation and which they regard as absolute truth. They then reason logically and without experimenting and from deduction to deduction they succeed in building a system which is logical, but which has no sort of scientific reality. Superficial persons often let themselves be dazzled by this appearance of logic; and discussions worthy of ancient scholasticism are thus sometimes renewed in our day."

CONCLUSIONS

I suggest that since the double-blind method for testing drugs has never been rigorously tested in the laboratory,
i.e. has never been validated or calibrated; is not based upon mathematical theory acceptable even to mathematicians; sets two important therapeutic variables at unreasonably minimum levels; is ethically questionable; cannot be used for comparing small heterogeneous groups; and has not led to the development of any useful new therapies, at least in psychiatry, it should be re-examined seriously to see if these important flaws can be corrected.

Other studies critical of double-blind controlled experiments are given in the list of references 4-10, 19

Summary

Controlled experiments may be conducted without the use of double-blind techniques, which themselves induce new difficulties and errors. In view of their wide acceptance as an indispensable tool in therapeutic trials, double-blind techniques should be critically re-examined because their value has never been rigorously tested in the laboratory, they are based upon unacceptable mathematical theory, they diminish the effectiveness of two important variables in any therapeutic situation (the faith of the patient and the doctor in the therapy), they are ethically questionable, they cannot be used for comparing small heterogeneous groups, and they have not led to the development of any useful new therapies, at least in psychiatry.

Resume

Des experiences controlees peuvent etre effectuees sans recourir aux methodes a double iconnu, lesquelles font naître de nouvelles difficultés et introduisent de nouvelles erreurs. Etant donne leur emploi generalise, comme outil indispensable Bans les essais therapeutiques, il serait bon de reexaminer dans un esprit critique les methodes A double inconnu. Leur valeur n'a jamais ete rigoureusement mise A l'épreuve en laboratoire; elles sont barks sur une theorie mathematique inacceptable; elles reduisent l'efficacite de deux variables importantes dans une situation therapeutique quelconque (la confiance mise, et par le malade et par le medecin, clans le traitement luiemme); elles sont discutables sur le plan de l'éthique professionnelle; elles ne sont d'aucune utilite pour comparer de petits groupes heterogenes et, enfin, elles n'ont jamais permis de mettre au point une therapeutique utile, du moms en psychiatrie.

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SOME PROBLEMS OF STOCHASTIC PSYCHIATRY
A. Hoffer* and H. Osmond**

Hogben (1957) reminds us that probability theory was developed to benefit noble English gamblers who hoped to increase their winnings at the tables. These early statisticians were dealing with man-made objects (dice, wheels, cards, etc.) built to certain exact specifications of size, symmetry, density, hardness, etc. Hogben writes “a calculus of probability is relevant to the real world (a) only insofar as it specifies frequencies of observable occurrences in an indefinitely protracted sequence of trials, (b) only if also such occurrences collectively constitute a sequence wholly devoid of order.” The calculus of probability was first used in physics and chemistry and later adopted by scientists who work with plants, animals and humans. One of its earlier applications to human affairs was in insurance where large numbers of individuals or incidents were involved.

Psychologists who develop tests for intelligence, personality and aptitude also applied a variety of forms of statistical analysis, and they seem to have been useful here, but they have not always found statistical methods to be more effective than clinical methods. Meehl (1954), Sydiaha (1959) Hogben’s sharp criticism and the fact that statistical analyses are not always very enlightening when applied to clinical matters raises an important question. To what extent is the real world in which we live, work, become ill and die of a kind that can be analyzed accurately and objectively by methods which some statisticians believe can do just this? In other words, are the measuring devices which they would have us use more helpful than misleading on balance?

It is hardly surprising that clinicians have joined in the general fashion and psychiatrists too now cherish these mathematical devices. Only a few years ago those authors of medical papers who used statistics would explain such terms as "standard deviation" or "X degrees of freedom" for the uninitiated. Today, authors sometimes present statistics only, no longer bothering to include the data from which they were derived. This increasing interest in statistical methods has undoubtedly been fostered by the rediscovery of what has long been known, and has indeed been the stock in trade of quacks since time immemorial. This is that the simple act of giving something or doing something no matter what it is often produces astonishing effects on patients. Some procedures may be started or some drug prescribed and the patient improves. When this occurs without any consensus that the procedure produces its benefits or the drug its effects by some means understood by the profession at large, this benefit is often called the placebo effect. This refers to reactions which may be beneficial or harmful by chemicals "believed" to be inert. We use "believed" because the inertness of a substance can only be established empirically. There is no reason why the purest starch should not be harmful to some people and beneficial to others. These reactions may be termed positive or negative placebo reactions. In a recent paper, Hoffer and Osmond (1961), we have noted that some people do not respond with appropriate physiological or psychological changes to compounds long known to be active, and half jesting we have termed these obecalp reactions, (placebo in: reverse). The possibility that human subjects can react positively or adversely to drugs raises serious issues. The chief of these is whether the "blind" studies of a classical kind are applicable to drug effects. After many years of relatively uncritical acceptance by scientists, but private resistance from

* Director, Psychiatric Research Unit, Department of Public Health, located at University Hospital, Saskatchewan.
** One Cottage, Milford (near Godalming) England.

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clinicians, statisticians themselves and clinicians have raised these questions. This problem requires urgent and immediate examination by all scientists working with human subjects. Unless this is done, research in these matters may be seriously hampered because scientists are being encouraged to use inappropriate methods which nevertheless have received general assent. It is already apparent that some granting agencies make this new fashion a necessary preliminary for getting money for research, yet as we shall show, it is at least possible that double-blind studies will as often indicate that an active compound is inactive as the converse.

Grayson (1961) has given an admirably clear account of the views of those who use double-blind techniques to test new drugs in psychiatric practice. At a symposium on Chlordiazepoxide he criticized severely papers given there and elsewhere. According to him, no study can be termed confirmatory unless it includes: (1) a controlled group of patients; (2) an objective evaluation procedure; and (3) compliance with statistical requirements.

Dr. S. Cohen voiced a different sort of dissent saying, "I would rather see a dirty study by Fritz Freyhan than a clean double-blind study by many other individuals." He added that dirty studies had shown certain chemicals to be effective many years ago and that classical double-blind studies in Veterans Administration Hospitals had merely confirmed what was already well-known.

The clinician and the statistician were at loggerheads, the statistician stating bluntly that he alone was correct, and the clinicians expressing a dour unwillingness to give up their ways which they believe have worked. Although Grayson did not actually say that all errors could be resolved by using the classical double-blind experiment which he had described, he clearly implied this, but in company with most other theorists in experimental design, he had neglected patients' failure to react to chemicals which are known to be active in most people. We will therefore see what happens to his sort of experimental design which is so highly recommended by theorists today when one does take this into account.

Treloar (1939) describes two classes of erroneous inference (A) where insufficiency is found when there is in fact a real difference, (B) where significance is claimed when none in fact exists. Class A errors lead to valuable procedures or active pharmacological substances being either ignored or improperly discarded, thus increasing or prolonging human suffering unnecessarily. Class B errors lead to the use of ineffective treatments when better may be already available or could perhaps be devised. In addition, they may result in wasteful and expensive investigations in the future. Treloar believes that Class B errors are more harmful to the progress of science.

Treloar states that the price for avoiding one sort of error must be to increase the chance of the other sort. It is a matter of debate which class of error has the graver consequence for medicine. It is by no means certain that Treloar's verdict holds equally in every scientific situation, for sometimes errors of the second sort (mistaking a positive result for a negative) may be by far the more serious. The great blood-letting epidemic of the eighteenth century certainly shows that harm results when significance is claimed where none exists. Generally speaking, unless the treatment itself is dangerous little damage is done; even if a particular medicine does no good it at least gives patients, their relatives and doctors, a feeling that something is being done which may tide them all over a difficult time. If, however, insignificance is alleged when in truth the treatment or substance is effective, then we run a certain risk of not discovering an insulin or penicillin. That this is no idle notion can be shown by the fact that it actually happened with penicillin itself. Ernest Augustin Clement Duchesne in 1897 wrote his doctoral thesis on antagonisms.
between microbes and moulds. (See M.D of Canada, January 1961). He concluded "Furthermore, it seems from some of our experiments, unfortunately too few in number and which ought to be repeated again and checked, that certain moulds (penicillus glaucum) inoculated into an animal simultaneously with extremely virulent cultures of certain pathogenic microbes (E. coli and Ebarthella typhosa) are able to attenuate the virulence of such bacterial cultures to a remarkable degree. It is to be hoped therefore that in pursuing the study of the facts of biological competition between moulds and microbes—merely outlined by ourselves and to which we have no claim other than rendering here a very modest contribution—the discovery of further facts directly useful and applicable to prophylactic hygiene and therapy may be attained. Duchesne's work passed completely unnoticed at the time and was soon forgotten. It is therefore particularly important not to jump to hasty negative conclusions, because it frequently happens that an initial substance which either has side effects or is not notably potent can be a stepping stone to something both safe and potent. What has saved useful substances and procedures in the past has often been simply the faith of a few committed people. There is a real danger that the rash pontifications of dedicated methodologists may be enough to destroy the faith at a crucial moment.

Model Error

There is another kind of error which has crept into psychiatry in evaluating the results of therapy from a long-term point of view. This kind of error has been directed against the evaluation of the shock treatments, especially ECT and insulin shock therapy. Penrose and Marr (1943) evaluated insulin shock then being given in the Province of Ontario, and concluded that the outcome of this treatment, as measured by the number of patients in hospital at the end of four and five years, was no different from those who had not received it. They therefore inferred that it was pointless to use insulin as a treatment for schizophrenia. Clinicians, however, seem to have paid no attention to their advice for if anything, more deep insulin was given after their paper than before it. Insulin was not discarded until safer and simpler treatments such as the phenothiazones became available. The clinicians' reluctance to relinquish insulin is sometimes used as an example of obstinate and supercilious behavior, but it might also mean that those who work closely with patients were better able to assess what had happened than statisticians working with data.

In our particular example, the clinicians may have been well advised to continue to use insulin, for we believe that the statisticians made a serious mistake which has gone unnoticed for nearly 18 years. They did not ask themselves relevant questions about the kind of illness which they were examining. In other words, they used the wrong sort of model with which to determine whether treatment was successful or not. There are at least three kinds of models which are useful for thinking about diseases and their treatment. The first is that of a single attack. Pneumonia is such a disease. Often in these cases, the body is overwhelmed by the intrusion of the foreign organism but, having thrown off the assault, it seems to be resistant to any recurrence of the same disease.

A second class of disease is one in which there is a phasic course of the illness with exacerbations and remissions. Such a disease is, for example, arthritis.

A third kind of model is where the disease is continuously present and unless adequately treated, may lead to quick death. For example, pernicious anemia or diabetes mellitus. In assessing the response to treatment, one must know which model is most appropriate for a particular disease. Schizophrenia, being a very variable disease, may follow any one of these three models and therefore the type of evaluation must be
quite different for each case. If schizophrenia were like pneumonia and were produced by a massive attack from a single organism, then one would expect a specific treatment to quickly vanquish the organism, and if four or five years later another attack produced a relapse, one would not state that the original treatment had been ineffective. One would merely be disappointed that the disease had recurred and would give the same treatment again. If schizophrenia were an illness like arthritis, even when there was a good response to treatment, one could never be quite sure that this was not one of those natural remissions which do occur.

The third model, the chronic disease, is the easiest to work with, especially when one has a treatment which is quite specific. This is because here treatment is followed quickly by remission and ceasing treatment results in recrudescence of the illness and this can be repeated until the investigator is certain that a relationship exists between treatment and remission.

It is clearly possible to treat a large group of patients, to have a good remission of symptoms and to find after some months or years have passed that all or many of them have relapsed. And since with the control group of patients, there would also be remissions and exacerbations, it is likely that in an illness of this kind, regardless of treatment given, the same proportion of patients would suffer relapse four or five years later without further treatment.

If schizophrenia is a chronic disease and most people think it is, then it would be unreasonable to expect any treatment, however successful at first, to continue to exert a beneficial effect for an indefinite time after that treatment had been stopped. If schizophrenia is a chemical disease, then one would expect a response to treatment resembling that of other biochemical diseases.

For the last nine years we have studied the effects of massive nicotinic acid and its amide on schizophrenic patients. We have found that those patients who have been given ECT and nicotinic acid show a very small number of readmissions during the first few years after discharge compared with those who have not had this vitamin, but the protective action only seems to last for about two to three years. After this, those patients who have benefited greatly from nicotinic acid slowly begin to relapse. An account of this in which the data is given in detail has been published by C. C Thomas in a book entitled *Niacin Therapy in Psychiatry*. A similar group of schizophrenic patients given ECT but no nicotinic acid had a remission rate of 50 to 60 percent within the first one to two year periods after discharge, but over the next four, five or six years this did not greatly increase. Those not receiving nicotinic acid had a downward concave curve while those who had it show an upward concave curve. This data is shown graphically in Figure 1.

**FIGURE 1**

![Graph showing comparison between two groups of patients](image-url)

<table>
<thead>
<tr>
<th>Year</th>
<th>Group A (ECT)</th>
<th>Group B (ECT + Nicotinic Acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>1954</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>1955</td>
<td>0.00</td>
<td>0.00</td>
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</tbody>
</table>

Number of schizophrenic patients readmitted at least once during a follow-up period.
these groups depends upon which year is selected after discharge. As it happens, with these patients the differences are significant for all years, but if curve B continues to follow its trend and curve A remains stable, then in a few years’ time the same proportion of patients will have been readmitted from each group. One could perhaps select a ten-year follow-up and show no difference whatever then. Suppose we had known nothing about our patients’ progress during this decade, and had undertaken our follow-up at the end of it, we might have well concluded, quite erroneously, that niacin was useless. Our statistical conclusions would be correct but wholly misleading. In these patients, nicotinic acid was given for at least one, and sometimes for several years. It exerted a protective effect against recurrence of schizophrenia which was sustained long after it had ceased to be given. Other substances might work in much the same way, but be of a kind which could only be given in a hospital. Insulin coma treatment seems to be of this type. We have still to be convinced that the many able clinicians who reported on the successful use of insulin were all self-deluded. As we have already noted, psychiatrists using insulin in the treatment of severe schizophrenia discontinued its use only upon the development of other treatments which were almost as effective as ECT, reserpine and tranquilizers, and which were simpler, safer and easier to administer. Some mental hospitals still use insulin and report upon it favourably. Since it is possible that this misunderstanding originated in Penrose and Marr’s paper, it should perhaps be carefully re-examined for it has had great influence and not determining what had happened historically is important. Their error lay in the first, second and third years after treatment. It is quite possible that there were significant differences here which escaped them. The selection of the fourth and fifth years was quite arbitrary, indeed Penrose and Marr give no adequate reason for choosing this time rather than some other. Statistical errors of inference of the second sort are more likely to occur unless proper follow-up assessments are used.

One of us (H.O.) has been involved recently in an interesting example of an error of the second sort in connection with a study of ololiuqui. Osmond25 made the first psychiatric study of the psychotomimetic properties of ololiuqui, long known as the chief narcotic of the Aztecs. After a series of self experiments with increasing doses of ololiuqui (Rivea Corymbosa) seeds, he reported definite and an unexpected kind of activity, i.e., psychological changes and apathy followed by a marked feeling of well-being. This report was received with some excitement and studies of its psychological properties and attempts to isolate the active fraction began.

Investigators at Lexington21 ran a classical double blind study, and Kinross-Wright22 conducted a single blind experiment. Neither found any convincing evidence that ololiuqui was a psychotomimetic agent. It now appeared that Osmond had made a serious error due to his somewhat subjective method. The chemical studies were more productive. In 1960, Hofmann (discoverer of LSD-25 and psilocybin) reported at a symposium in Australia that he had isolated an indole alkaloid, lysergic acid amide from Rivea Corymbosa (ololiuqui). Further, he had consumed a small quantity of this alkaloid and had experienced a reaction similar in many respects to one Osmond had experienced in 1954. Hofmann’s report was received with great skepticism by some chemists who stated that they had been unable to find these alkaloids in ololiuqui and assumed that this meant that no one else could find any. Lysergic acid alkaloids had until now been found only in some fungi and not in higher plants, so this claim of Hofmann’s was doubly exciting. Taber and Heacock30 corroborated Hofmann’s claim and have isolated lysergic acid amide (L.A.) as well as other substances. Since L.A. is known to be a weak psychotomimetic, the original work of Osmond is now verified.
from this that even very competent and experienced investigators are not guaranteed success by using methods which are often discussed as if they alone can guard against error.

There is another matter, not illustrated by the ololiuqui example but which is, we think, important. This concerns the way in which scientists perceive each other. Is it better for science if scientists try to corroborate each other or try to destroy other scientists' work? Although one might suppose that either method would yield much the same results, there are great practical differences. It may be that in psychiatric research a number of those ostensibly engaged in it do not know that the effort of corroborating another's work is frequently as onerous as that of original discovery. It is indeed for this very reason that men who do this are so highly regarded by their fellow scientists. It seems proper to ask ourselves what motives are likely to be the best for undertaking a task which is of the highest importance, calls for great exertion and yet which lacks the special spice and excitement of original discovery. Much must surely depend upon the attitude which one scientist has towards another. It has long been our tradition, rarely broken, for scientists to accept their peers as being men of honesty and integrity although always being ready to disagree with their inferences and their conclusions unsparingly. Polemic has been the life blood of science, but generally speaking, character assassination has been less well regarded. Attempts to corroborate must be persistent, cautious, sustained and only after determined attempts to corroborate would a negative report be made. No such report should ever be made unless the procedure originally described had been used with exactness. This still seems to be the best method to us. We believe that one should have faith in the resourcefulness, skill and honesty of other research men combined with a rigorous and prolonged investigation of their claims and readiness to disagree when necessary. Unfortunately another attitude seems to be not uncommon in psychiatric research where the discoverer is often assumed to be foolish, brash, crack-potted and even a little crooked at times.

Some behave as if they believed that the best attitude towards their fellow researchers was one of suspicion or even hostility. They do not act as if they were attempting to corroborate or confirm another's work, but to disprove it or expose some trick or stupidity. This attitude is common among certain kinds of inspectors whose function is to find evidence for misdeeds and here it is doubtless proper, but is this an attitude which we can afford to foster in the scientific community of psychiatric researchers? For with a negative and inspectorial attitude the scientist, supposedly trying to confirm original work, may be tempted to publish findings as a refutation of that work without the infinite patience, care and zeal exerted by the original discoverer. In effect, a lack of trust in the integrity of a fellow-scientist may lead to one giving up the search far too soon. In this way, science can be done great disservice and patients damaged. Readers of psychiatric journals will come across many examples of this kind of study in the literature of the last decade. Indeed, some researchers seem to make an occupation of "inspecting" other people's claims and failing to validate them after cursory efforts, thereby establish for themselves a reputation for "soundness." At times one wonders if this is not becoming a more acceptable way of being recognized as a psychiatric researcher than by attempting the onerous task of new discovery. We think it may be important for researchers to enquire whether they are conforming to those customs which have been found useful and productive in other branches of science. In contrast to Engel, we hold that one of the scientist's main tasks is to question the ideas and inferences of other scientists. Discussion, polemic, satire are entirely proper here. Let us have the strongest disagreements, but no ad hominem.
attacks, character assassinations, imputations of dishonesty or incompetence, and above all no inspector complexes. Eminence in science is conferred by one's peers, it does not descend on a man simply because he is the head of an institute, a department, a section or a laboratory. It inheres in men and women, not in the position which they chance to hold in an organization. Research does not require superscientists to decide what is and what is not; the scientific method and the passage of time will do that soon enough. There is the even greater danger that the inspectors will insinuate themselves into the councils of fund-granting bodies and with their passion for neat, clean and tidy experiments do psychiatric research untold harm. Indeed, they may already have done some. What has happened is that a confusion of function has arisen. It is far easier to be a capable inspector than to be a good judge of what is likely to be a valuable research and to increase our knowledge. It happens that it is this more difficult function that is needed most.

The Relationship of the Experiment to the Investigator

Foulds surveyed the literature on double blind studies. He found that significantly more double blind studies showed drugs to be ineffective than single blind. Fox, surveying a different set of studies, came to the same conclusion. Fox collected many reports on treatment, and by selection reduced them to a series of papers which he divided into those he considered had used acceptable methods and those which had not. Each classification was further sub-divided into two sub-groups. In one, the results suggest that a therapeutic drug was significantly better than chance (or faith). In the other, negative results were found. Papers with adequate controls (comparison groups) in which adequate statistical analyses had been used were classified as acceptable. This is what Fox found:

<table>
<thead>
<tr>
<th>Kind of Study</th>
<th>Drug</th>
<th>Therapeutic Claims</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Drug Effective</td>
</tr>
<tr>
<td>Acceptable</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Not Acceptable</td>
<td>20</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Drug Not Effective</td>
</tr>
<tr>
<td>Acceptable</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Not Acceptable</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Chi Square = 8.54, i.e., the null hypothesis was disproven. In other words, there was a significant difference in the conclusion of the two kinds of papers.

But Glick and Margolis found that the duration of clinical studies confounded these results. Although double blind studies showed significant differences less frequently they were more often of brief studies. Only one out of eleven double-blind studies was of long duration. But 12 out of 16 single blind studies were long clinical studies (Chi Square = 8 ca). Long-term studies more often reported clinical improvement than short-term double blind studies. They stated “there is no valid theoretical or scientific reason why double blind studies must be short-term or even placebo controlled or why single blind studies must be long-term or non-placebo controlled.” Finally from their extensive review of the literature, these authors could find no support for the common belief that initial enthusiasm for a particular drug is always followed by a later realism and a more sober evaluation.

Why, then, do people who carry out orthodox clinical studies seem to get better results than investigators who run double blind studies?

1. Fox considers that authors may be reluctant to write and editors even more reluctant to publish negative results. This may have once been true, but Fox's own collection of papers hardly suggests that this is so now. We have found few signs that authors are unduly sensitive or angered by negative results, rather the reverse. Indeed, one sometimes has the feeling the investigators have become so interested in method that the success or failure of a research is equated with a nicety of design rather than with new
discovery

(2) We believe that double-blind studies may prove drugs ineffective, i.e., have large errors of the second kind.

(3) What has usually been much neglected is the impact upon the investigator and thus on his staff and patients of the particular design followed. Barber in a witty study has dealt with this in a general way.

In any therapeutic study a variety of controls are required. It is not, of course, true that a controlled study is always one where a comparison group is used. Controlled studies are used in all the sciences. In biochemistry, a controlled experiment is one in which major variables such as temperature, pressure, concentration, pH are set at steady levels while other variables are allowed to fluctuate. But in clinical practice "controlled" has come to mean the use of a comparison group. It would be more accurate to call these studies comparison studies for such studies with two or more groups may ignore important variables such as drug dosage, its relationship to maximum need, etc. In fact, comparison studies may be nearly uncontrolled and those without a comparison may be very meticulously controlled.

One of the main variables which psychiatric investigators have tried to control has been called faith, suggestion, placebo effects, etc. Mathematicians have implied that the classical double-blind study will in fact do this. The mathematician may be correct, but he does not concern himself with the level at which faith is "controlled." A chemist, for instance, can control temperature at freezing or at boiling point. It makes little difference statistically unless one is interested in temperature as a variable and not as a constant. The chemist will therefore select that temperature which is most efficient for obtaining his particular objective.

One may perhaps excuse the statistician for his lack of understanding about faith as a variable, but we can hardly excuse those investigators who follow his recipes so blindly.

For faith can be made constant at a low level or a high level, yet the double blind technique usually sets it at a constant low level. But faith is an important ingredient in any therapeutic process, and if this is so, why not set it at the most effective level? Indeed as doctors, we are ethically bound to do just this, particularly when so far as the statisticians are concerned the results are the same so long as the faith level is constant. The investigator then wishes to show that faith plus a drug is significantly better for a patient than faith plus a placebo. As Hogben and Wrighton aptly point out, this is not usually done because "The reason is that cookery book recipes will commonly prescribe as the appropriate null hypothesis the one which commends itself to the mathematician for reasons which have nothing to do with the operational intention of the scientific worker."

The mathematician little interested in faith except to exclude it, cannot know that human nature being what it is, doctors prefer to know what their patients are getting and that there is some therapeutic benefit. And this is where we run into a major problem, because it is so difficult to ensure maximum but equal faith for both groups with double blind studies. This difficulty is readily explained on operant conditioning theory.

One important ingredient for maintaining a satisfactory relationship between doctor and patient is what amounts to positive reinforcement of the doctor himself by what appears to be successful treatment. When a doctor gives medicine to a patient and the patient seems to benefit, this reinforces (encourages) the doctor who heartens and supports the patient to continue taking the medicine. Such encouragement may in itself minimize side effects. Being reinforced by his success with one patient, the doctor will use the treatment on others with even greater confidence, and so a fruitful combination of medicine and faith develops. On the other hand, if many patients fail to respond, or
if there are side effects which disturb both patients and doctor, then the doctor's habit of giving that particular treatment will be extinguished quickly; indeed, it is something of a joke among those who often use new drugs that if one of them is to be successful, it is essential for the first few patients to do well, for this produces enough reinforcement to ensure continuing trials. It is obvious that the reverse can occur. A clinician may have negative reactions to an active drug and his faith in the drug can be as quickly extinguished. Originators of newer treatments are often sustained by their hypotheses. But the fact remains that clinicians have introduced many treatments which work.

This suggests strongly that in clinical studies without control groups, due to reinforcement, active drugs will be used until replaced by something proven better; while the giving of inactive drugs will be quickly discontinued. It follows from this that clinical studies are those in which the doctor's habit of giving the drug has been reinforced. Studies of short duration are those in which the habit has been extinguished. The fact that studies are long suggests then that there has indeed been therapeutic benefit. Long studies may indeed be an index of therapeutic benefit. One could argue that non-specific remedies have been used for centuries. However, such remedies are not altered until better ones come along and many "non-specific remedies" have been found to contain greater or less quantities of active drugs.

The finding by Fox and Foulds may be due to this. It is at least possible that the use of drugs or treatments for long periods of time is a better index of their therapeutic efficiency than any measures yet available, for were this not so, their use might have been discontinued long ago in the manner which we have described. This should at least be considered by those planning clinical trials.

Epicrisis

If this is as obvious as we have suggested, why then has it gone unremarked for so long? It has, of course, been discussed repeatedly in the past, but possibly in recent years clinicians have become intimidated and muddled by the formidable mathematics and the imposing words which methodologists so often use. Kluger (1931) warned eloquently almost one-third of a century ago against applying refined mathematics inappropriately. Like a great brandy, his papers read even better after a few decades. We can only urge the stochastically inclined to meditate upon his ideas, but we cannot resist whetting their appetites with a few lines from his paper:

"We must start from the facts and somehow find the tools adequate for their investigation. If we find in psychology that certain dynamic systems, certain behavior units, exist to which we cannot do justice by pointing out the few mathematical relationships known at present; if, at the same time, there seems to be no hope whatever for increasing our knowledge of these relations or of relations found by other exact methods; then even the description of these behavior units by means of these 'exact' methods (not to mention a thorough scientific treatment) is inexact since the tools are totally inadequate. In such cases a 'type' may be far more 'exact' than an equation. Only one who thinks about method as something divorced from the facts and from the material at hand will doubt this statement. In closing we would like to call attention to the fact that physicists inform us that there are scientific procedures which enable us to test the validity of a proposition by reference to a single observation."

It may be that our old and discredited medical standby, the single case, will one day become respectable again. Others preceded Kluger with sensible warnings, none more eloquently than Claude Bernard whom Hogben quotes as writing almost a century ago, "By destroying the biological character of phenomena, the use of averages in..."
Physiology and medicine usually gives only apparent accuracy to the results. If, for instance, we observe the number of pulsations and the degree of blood pressure by means of the oscillations of a manometer throughout one day, and if we take the average of all our figures to get the true or average number of pulsations, we shall simply have wrong numbers. In fact, the pulse decreases in number and intensity when we are fasting and increases during digestion or under different influences of movement and rest; all the biological characteristics of the phenomena disappear in the average. If we collect a man's urine to analyze the average, we get an analysis of a urine which simply does not exist; for urine when fasting is different from urine during digestion. A startling instance of this kind was invented by a physiologist who took urine from a railroad station urinal where people of all nations passed, and who believed he could thus present an analysis of average European urine! Aside from physical and chemical, there are physiological averages, or what we might call average description of phenomena, which are even more false. Let me assume that a physician collects a great many individual observations of a disease and that he makes an average description of symptoms observed in the individual cases; he will thus have a description that will never be matched in nature. So in physiology, we must never make average descriptions of experiments, because the true relations of phenomena disappear in the average. I acknowledge my inability to understand why results taken from statistics are called laws. Certain experimenters, as we shall later see, have published experiments by which they found that the anterior spinal roots are insensitive; other experimenters have published experiments by which they found that the same roots were sensitive. These cases seemed as comparable as possible; here was the same operation done by the same method on the same spinal roots. Should we therefore have counted the positive and negative cases and said: The law is that anterior roots are sensitive, for instance, 25 times out of a 100? Or should we have admitted, according to the theory called the law of large numbers, that in an immense number of experiments we should find the roots equally often sensitive and insensitive? Such statistics would be ridiculous, for there is a reason for the roots being insensitive and another reason for their being sensitive; this reason had to be defined; I looked for it, and I found it; so that we can now say: The spinal roots are always sensitive in given conditions, and always insensitive in other equally definite conditions.

Hogben comments, "Against this background of lucid exposition (1865), it is at first difficult to understand why it should now (1954) be necessary to challenge the claim of the statistician to prescribe the design of experiments in general and of the clinical trial in particular. In my view, such claims are acceptable only if we relinquish the standards of intellectual rectitude of an earlier generation."

And again, "In short, statistical theory is temporarily, at least, in the quicksands. Nothing less than a transvaluation of all values is in process. For my part, I have reluctantly come to the conclusion that the statistician will emerge in the end with a very much chastened view of what traditional methods can accomplish. If there proves to be any enduring basis for a stochastic calculus of judgments, we shall be able to define its proper terms of reference clearly only after we have cleared the site from an overgrowth of prescriptions which can certainly no longer claim the universal assent of professional mathematicians."

And, "If we then concede every claim put forward for such devices as the Chi Square test and others of its kind till recently prescribed by most professional statisticians without misgivings, we may still entertain misgivings about how far the questions for which they claim to prescribe the method prerequisite to a correct answer tally with what the clinician and the biological research worker do want or should most want to..."
know in the context of the clinical trial. In stating my own view about this, I approach the topic with the admitted preoccupations of my main professional lifework as an experimental biologist. In that capacity, I see the assessment of remedies as the disclosure of a specific stimulus-response nexus; and I mean by controlled experiment no less exacting an undertaking than as stated in my opening paragraph. Hogben and Wrighton summarize their point of view in this way: (1) Hitherto it has been customary to assess the claims of therapeutic and prophylactic measures in statistical terms by recourse to tests which invoke a unique and so-called null hypothesis, namely that the procedures compared are equally efficacious (2) This procedure has no bearing on the operational intention of the trial, viz to find out how much advantage accrues from substituting one treatment for another. (3) Within its more restricted domain, the credentials of any significance test which takes within its scope only one hypothesis have now to meet the criticism that it takes into account only one sort of error, viz that of rejecting the hypothesis, when it is true (4) A procedure which justifies assertions of so limited and conditional a scope may be a useful self-disciplinary convention; but its claims to rank as an instrument of statistical inference are no longer acceptable.

It may be however that there is something about statistical experiments which Bernard, Klüver and Hogben have all failed to appreciate. We shall attempt some sort of empirical test. One of our earlier arguments could perhaps be turned against us—in the form that since many people use and are enthusiastic about the statistical methods they must be effective. We noted that doctors use certain medicines and procedures for long periods of time because these result in their being reinforced by their patients' betterment and tend to relinquish those which do not result in improvement. In double blind studies, those who undertake them seem to be reinforced (rewarded) by the elegance or cleverness of the design rather than by any real or supposed benefit to patients. Such studies as Fox's scholarly enquiries showed that they are their own reward, but in our present climate they reap in addition a harvest of praise from critics, like Dr. Grayson, who admire the new mode and scorn the old. If learning theory is any guide, these self-rewarding studies will continue until there is a marked change of medical opinion regarding their worth.

Some other test than this is needed. We could enquire for instance how often elaborate statistical manipulation and the methodological refinements now considered essential for good psychiatric research, have played a large part in those developments of the biological sciences which have done so much to improve the human condition in the last century. Few would disagree that Nobel prize winners are a fair sample of those who have made great discoveries. According to Stevenson's (1953) survey fifty-eight Nobel prizes were given for discoveries in the biological sciences between 1900 and 1950. Table 1 shows how they were distributed.

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunology and Bacteriology</td>
<td>10</td>
</tr>
<tr>
<td>Physiology</td>
<td>12</td>
</tr>
<tr>
<td>Anatomy and Pathology</td>
<td>4</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>18</td>
</tr>
<tr>
<td>Genetics and Embryology</td>
<td>3</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology and Otolaryngology</td>
<td>2</td>
</tr>
<tr>
<td>Therapeutics</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
</tr>
</tbody>
</table>

It appears from Stevenson that only one (Muller) made any extensive use of statistics, and this was in genetics. None of them referred to statistics in their main work. None of the eight prize winners in therapeutics used the double blind...
method now thought to be so indispensable. This can hardly be because statistics are new; Galton and Pearson did much of their valuable work in the last quarter of the nineteenth century, Fisher (1925) in the first quarter of the twentieth. Statistics of this kind are as old as bacteriology and immunology and far older than biochemistry founded by Gowland Hopkins about 1912. In spite of its recent origin biochemistry in which statistics play a very small part heads the list with eighteen prize winners, almost one-third of the whole. It seems from this empirical test that statistical expertise has little to do with original discovery. Those who put their faith in it should consider these findings before becoming too over-bearing and insistent that their’s is the only path to truth.

Let there be no misunderstanding. We do not imply that stochastic theory should dispense with statistics or that scientific methodology should be neglected. It is and must continue to be a valuable aid which can ease the burden of discovery and speed its confirmation and acceptance. But sometimes it has become a straight-jacket, even a coffin, imposing harmful and fatal limitations on those delicate tendrils of enquiry which are among the most precious growths of science. Clinical trials should be done cautiously and with modest expectations. We should not be too keen to discard or deride substances or treatments which experienced clinicians say help their patients. They may, after all, be right.

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SECTION VII—Efficacy and Toxicity

The double-blind controlled method for testing efficacy is only one of a number of possible tests. In spite of its overwhelming popularity, especially among professors, editors, and civil servants; there is a large and growing body of scientific opinion that it has many inherent errors and should be used with great scepticism and its limited conclusions accepted with extreme reluctance. When it comes to a matter of toxicity, no double blinds are recommended. This is too serious a matter to be left in the hands of double-blind methodologists. We do not know of a single drug taken off the market because of double-blind human trials. We believe this double standard tells us much about the validity of the double blind. For serious matters such as toxicity, it is ignored. For efficacy, obviously considered much less serious, it is recommended.

How then are we to judge the relative toxicity of drugs? We cannot demand animal type toxicity trials where the lethal dose is determined by finding out how much will kill half the subjects. We are forced to fall back on the number and intensity of undesirable side effects and reactions which would be very toxic and even lethal if allowed to continue.

Children, Drugs, and Vitamins—A Matter of Ethics, A. Hoffer, M.D., Ph.D.

When Dr. H. Osmond read Dr. B. Rimland's megavitamin study on a large series of sick children, it occurred to him that it lent itself to an examination of efficacy as against toxicity. Efficacy would be the improvement due to the drug while toxicity would be the term applied to any worsening of the condition. Relative efficacy would be the ratio of one to the other. Thus if drug A helped 50 percent of a sick population and made 10 percent worse, its relative group efficacy would be 5. If it helped 25 percent and deteriorated 25 percent, its relative group efficacy would be 1. Obviously the drug with highest relative efficacy would be the one best used for most sick children.

Rimland (1972) reported results which make it possible to rate a large number of compounds. His Table 2 is here reproduced:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Total No Definite Effect</th>
<th>Possibly Helped a little</th>
<th>Total</th>
<th>Some Impr Def. Helped</th>
<th>Total</th>
<th>Made a Little worse</th>
<th>Made Much Worse</th>
<th>Total</th>
<th>Efficacy Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexedrine</td>
<td>172</td>
<td>30</td>
<td>18</td>
<td>48</td>
<td>25</td>
<td>19</td>
<td>44</td>
<td>27</td>
<td>80</td>
</tr>
<tr>
<td>Aventyl</td>
<td>35</td>
<td>16</td>
<td>5</td>
<td>21</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Benedryl</td>
<td>151</td>
<td>47</td>
<td>45</td>
<td>92</td>
<td>13</td>
<td>21</td>
<td>34</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Compazine</td>
<td>49</td>
<td>15</td>
<td>16</td>
<td>31</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Deana</td>
<td>73</td>
<td>30</td>
<td>16</td>
<td>46</td>
<td>10</td>
<td>7</td>
<td>17</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Dilantin</td>
<td>204</td>
<td>69</td>
<td>36</td>
<td>105</td>
<td>18</td>
<td>39</td>
<td>57</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Mellaril</td>
<td>277</td>
<td>66</td>
<td>61</td>
<td>121</td>
<td>57</td>
<td>44</td>
<td>101</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Stelazine</td>
<td>120</td>
<td>25</td>
<td>27</td>
<td>52</td>
<td>20</td>
<td>20</td>
<td>40</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Thorazine</td>
<td>225</td>
<td>49</td>
<td>50</td>
<td>99</td>
<td>25</td>
<td>33</td>
<td>58</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Valium</td>
<td>106</td>
<td>28</td>
<td>16</td>
<td>44</td>
<td>9</td>
<td>22</td>
<td>31</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Ritalin</td>
<td>66</td>
<td>7</td>
<td>10</td>
<td>17</td>
<td>10</td>
<td>12</td>
<td>22</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>52</td>
<td>11</td>
<td>10</td>
<td>21</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Ataraz/Vistaril</td>
<td>51</td>
<td>15</td>
<td>12</td>
<td>27</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Mysoline</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

TABLE 2
Rimland wrote, "Table 2 shows for the total group of children that certain of the drugs (e.g., Dexedrine) seem to impair behavior more than they help, while other drugs (e.g., Mellaril) are more often beneficial than harmful. Half of the drugs appear to have harmed more than helped, and even Mellaril was reported to have helped only about one-third of the 277 children on whom it was tried."

We have added the relative efficacy numbers calculated by dividing the number of children who were definitely helped or showed improvement by the number of children made a little worse or made much worse.

Rimland states: "It is interesting to compare the drug results in Table 2 with the results of our so-called 'megavitamin' study. The megavitamin study involved several hundred children who were given large amounts of vitamin 'C' and certain of the B vitamins, especially niacin, B6, and pantothenic acid. The vitamins were given for a three-month period, followed by a one-month 'no-treatment period.' Evaluations of change were made by each child's parents and his physician.

"Table 3 shows that the vitamins are not only far more likely to help than the drugs—they are also far less likely to cause any kind of harm—behavioral or physical.

"The findings in Table 3 are of special interest in view of the criticism of our vitamin study commonly made by people who do not understand the experimental design of the study. The study made use of an unusual design in which clusters of children, grouped by a computer in terms of their similarity on Form E-2, were compared on their response to treatment. The computer grouped the children with no information on their response to the vitamins. The criticism was that our positive results might stem from the fact that many parents would be inclined to overrate the vitamins because they want so badly to see their child improve. This criticism is not valid, but if it were valid, the same spurious effect should be seen in the parents' assessment of the drugs. It is not. Since there is clearly much more improvement reported for the vitamins than for the drugs, the argument must be rejected that our vitamin findings reflect only wishful thinking by the parents (As indicated in our primary report on the megavitamin study, the finding of significant between-cluster differences in response to the vitamins leads to the same conclusion [Rimland, 6]).

"I predict that in a few years the use of high dosages of vitamins will be a common-place method of treating—and preventing—various disorders, including especially the so-called 'mental' disorders. There is a very common misconception to the effect that anyone who eats a normal diet will not require additional vitamins. That may (or may not) be true in most cases, but it is certainly not true in all cases."

### Table 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>No Def Effect</th>
<th>Possibly Helped a Little</th>
<th>Some Impro</th>
<th>Def Helped</th>
<th>Total</th>
<th>Made a Little Worse</th>
<th>Made Much Worse</th>
<th>Total</th>
<th>Efficacy Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drugs</td>
<td>1591</td>
<td>402</td>
<td>324</td>
<td>726</td>
<td>202</td>
<td>238</td>
<td>440</td>
<td>209</td>
<td>216</td>
<td>425</td>
</tr>
<tr>
<td>Avg Drug</td>
<td>100%</td>
<td>253</td>
<td>203</td>
<td>456</td>
<td>127</td>
<td>149</td>
<td>277</td>
<td>131</td>
<td>136</td>
<td>267</td>
</tr>
<tr>
<td>Best Drug</td>
<td>277</td>
<td>60</td>
<td>61</td>
<td>121</td>
<td>57</td>
<td>44</td>
<td>101</td>
<td>31</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Mellaril</td>
<td>100%</td>
<td>217</td>
<td>22</td>
<td>43.7</td>
<td>206</td>
<td>158</td>
<td>364</td>
<td>112</td>
<td>87</td>
<td>199</td>
</tr>
<tr>
<td>High dosage</td>
<td>191</td>
<td>20</td>
<td>37</td>
<td>57</td>
<td>41</td>
<td>86</td>
<td>127</td>
<td>4</td>
<td>3</td>
<td>180</td>
</tr>
<tr>
<td>Vitamins</td>
<td>100%</td>
<td>104</td>
<td>19.4</td>
<td>298</td>
<td>215</td>
<td>450</td>
<td>665</td>
<td>21</td>
<td>1.6</td>
<td>37</td>
</tr>
</tbody>
</table>
Thus it is clear that the megavitamin approach not only helped more children than the best single drug, Mellaril, but also had an efficacy index 10 times as high, chiefly because it produced so few side effects.

This then is the background for one of Dr Osmond's memos entitled "Children, Drugs, and Vitamins—A Matter of Ethics," which follows:

"You will see that Bernie R has now done this piece of computation with very interesting results. What I hope we shall be able to do is to underscore the facts which this very simple approach has made so very clear. All drugs may do nothing much, some good or some harm. The clinician aims at getting as much benefit as possible and as little harm. One would suppose that a rational approach would be to start with the best bet which would clearly be that which did most good and least harm. Because a substantial proportion of all these substances came into the 'nothing much' category, we need only study the worse and improvement categories. There is no reason why a drug should not have a 50 percent much worse or a 50 percent much better split, but none of these did. Clearly when this is likely to happen one must be very alert to deterioration and wherever possible discriminate between those who are likely to be benefited and those who are likely to be harmed.

"Bernie's figures allow us to construct a sort of rough cost-benefit approach. I shall exclude the no-change cases although they too could be examined and should be examined in a longer article.

"Where change occurs, Mellaril and the vitamins apart, it is as likely to be for the worse as for the better. This applies to both categories of improvement and worsening. With Mellaril the chances are 2:1 in favor of improvement; I am a poor statistician but go by Sir Ronald Fisher's rule, as told me by Leonide Goldstein, that in medicine the kind of statistics you need are those that don't require statistics. Mellaril looks better to me than the assembled drugs.

"However, when we come to the vitamins, the chances of being definitely helped are three times that of Mellaril while the chances of being made much worse are less than 1:25. If one concentrates on the definitely helped-much worse figures and compares Mellaril and vitamins and uses the product of these two categories, on my reckoning the vitamins are 12 times as effective as Mellaril, because they are (roughly) three times more likely to produce definite help and four times less likely to do harm.

"I do not know that medicines have ever been assessed in this way before, but it seems to me that an examination of this and other medical procedures in these terms would be possible and might throw a very different light on drug and other treatment effectiveness. My mathematical knowledge is so poor that I may have made some gross blunder here, but I am inclined to think that I have not done so. There are times when lack of sophistication allows one to recognize issues which would otherwise be obscure.

"As far as the patient and his/her family, what they are concerned with is a cost or risk-benefit which can be assessed fairly simply. To make that reasonable assessment, which NIH urges upon us as a right for all patients, one has to have some way of assessing and presenting the information available. I do not doubt that there are more elegant and efficient ways than those which I have suggested here, but since at this moment, so far as I know, no method of this kind is in general use, mine can stand until superseded. It has much bearing when it comes to measuring the nature and extent of improvements in medicine, surgery, etc. over the years.

"My own eye operations are examples of this (cataracts); 25 years ago or so the odds were not very much better than say 50 percent definite improvement against 50 percent complete loss of vision. The operation itself was frightening, sometimes very painful, psychotic episodes were not infrequent, and occasionally operation on one eye might result in complete blindness in both. Today the odds in favor of restoring vision are about
99:1, and the odds on losing one's vision have become miniscule. In other words, the benefits have increased greatly and the risks have been greatly reduced.

"There have been many similar situations, but in my experience medical matters are rarely presented in this manner. Were this done it might make it easier for us to discriminate among the various treatments available and allow doctors, patients, and their families to gauge realistically where the best course lay. This approach would also draw our attention to those illnesses in which the current natural history has been insufficiently investigated for us to be able to make a reasoned and reasonable decision regarding the chances that treatment will help rather than hinder." (B. Rimland, "Recent Research in Infantile Autism," Operational Psychiatry 3, 35-39, 1972)

One of the most dangerous side effects of tranquilizer therapy is a condition until now considered irreversible, tardive dyskinesia. Kunin (1976) referred to it as a prolonged and sometimes permanent extrapyramidal syndrome present in up to 50 percent of patients older that 50 who have been on tranquilizers over three years. Over 2,000 cases have been reported in the world literature by mid-1973. An FDA bulletin in May 1973 advised caution in the use of tranquilizers. It acknowledged that the symptoms appear to be irreversible in some patients and that there is no known treatment.

Modern psychiatry would collapse without tranquilizers. It is the main base for so-called "community psychiatry." Tranquilizers are very helpful when used in moderation wisely and as an adjunct to orthomolecular psychiatry. It is desirable to prevent the toxic side effects of which tardive dyskinesia is one of the worst.

Ironically, the solution may have come from orthomolecular principles. Kunin (1976) was spurred to investigate the cause of tardive dyskinesia by finding that 10 percent of his schizophrenic patients already were afflicted and by a report that tranquilizers bind manganese firmly (this is called "chelation") and could cause a manganese deficiency. Manganese is found in high concentration in the extrapyramidal system. It appeared likely that, by leaching manganese out of these parts of the brain, tranquilizers caused tardive dyskinesia.

Very soon after, Kunin was consulted by a young man who complained of dyskinesia due to fluphenazine enanthate. This condition had not cleared with previous medication. However, manganese chelate 10 mg three times per day cleared it in two days. In his report he gave details of 15 cases. These are Kunin's conclusions:

1. Fifteen cases of withdrawal and tardive dyskinesia were treated with manganese chelate, and 10 of these with niacin or niacinamide also.
2. Review of frequency of occurrence and mechanisms of cause and treatment in drug-induced dyskinesia are discussed.
3. There are four cases (27 percent) of dramatic and almost immediate cure, after manganese treatment. In nine other cases (60 percent) definite improvement occurred in two to five days. Only one case was unresponsive to manganese treatment.
4. In one case unresponsive to manganese, niacin therapy was dramatically successful, associated with almost complete cure in a matter of hours.
5. In eight of nine other cases in which niacin was used it was associated with significant elevation of mood and clearing of sensorium. In seven of seven cases that also were treated with niacinamide similar clearing of sensorium was noted and, in two cases, significant improvement in extrapyramidal symptoms.
6. It is concluded that manganese appears to be of value in many cases of tardive and withdrawal dyskinesia.
7. It also appears that manganese may be of value in preventing the occurrence of tardive and withdrawal dyskinesia.
8. It is likely that niacin and niacinamide are of some value in many cases of drug-induced extrapyramidal syndrome.
9. More extensive and better controlled
studies are needed to evaluate all of these observations and impressions.

One of us (AH) observed similar responses. It is now (AH) policy to use manganese in combination with zinc for any patient where there is any evidence of dyskinesia developing or present.

It is likely Kunin’s work will be confirmed when it is done by competent orthomolecular psychiatrists. His work suggests that tranquilizer preparations should contain enough manganese to prevent the production of manganese deficiencies.
SECTION VIII—Letters

April 14, 1971

Dr M A Lipton
Department of Psychiatry
University of North Carolina
CHAPEL HILL, North Carolina

Dear Dr Lipton:

I recently noticed with some surprise that you were Chairman of an APA committee given the mission of looking into the megavitamin B3 claims. You have clearly established yourself as a vigorous and unrelenting opponent of the use of this approach as is witnessed by your address to the symposium in California, by your press conference with APA Newsletter, and in your letters to Mr. J De Silva which you circulated widely.

In view of your known and evident bias against the use of vitamins I now ask you to disqualify yourself as Chairman. For any report coming from your committee with you as Chairman would properly be as suspect as a favorable report coming from a committee whose Chairman is a rabid enthusiast.

If you decline to accede to my request I will make this an official request to the President of APA, Dr R Garber. In order to acquaint him with my intention, I am sending him a copy of this letter.

To give him a complete record of your views, I also ask you to send him a copy of your letter to Mr. J De Silva in which I was slandered and a copy of my letter to you which you did not acknowledge. If you feel reluctant to do so, I will be pleased to send him copies.

Yours truly,
A Hoffer, M D , Ph D

AH:afm
cc: Dr R Garber
cc: Dr. H. Osmond

June 8, 1971

Dr R S. Garber, President
American Psychiatric Association
Carrier Clinic
BELLE MEAD, New Jersey 08502

Dear Bob:

Sometime ago I wrote a letter to Dr. Morris Lipton, the Chairman of a special committee to investigate the megavitamin claims, and I sent a copy to your office. So far I have not received any reply from Dr Lipton who seems to be a man who refuses to answer his mail.

I now write to you directly to protest his appointment as Chairman of a committee to investigate the megavitamin claims since he has already expressed himself publicly over the past year as being very much against the position of those of us who are using these treatments. I do not see how any Commission with such a Chairman at its head can possibly come up with a neutral and objective assessment.

For this reason, I therefore request you as President of the American Psychiatric Association to take action in connection with my request.

You realize, of course, that if you do not do so any report that comes out from this Committee will obviously be very biased and I, of course, will make it widely known that this is the case.

Sincerely,
A Hoffer, M D , Ph D

AH:afm
July 13, 1971

A Hoffer, M D , Ph D
1201 CN Towers, First Avenue South
Saskatoon, Saskatchewan
Canada

Dear Doctor Hoffer:

Several weeks ago I received your letter from Dr. Garber In your letter of June 8, you expressed some concern regarding the APA Task Force on Vitamin Therapy and the Chairman, who is Dr. Morris Lipton The Task Force members are Dr. Morris A Lipton, Chairman; and Drs Thomas Ban, Francis Kane, Jerome Levine, Loren Mosher, and Richard Wittenborn (consultant) The Task Force is responsible to the Council on Research and Development. The Council is presently composed of Dr. Sidney Malitz, Chairman; Drs. Monroe, Blueck, Hamburg, Schwab, and Shervington. Any reports that the Task Force prepares are first submitted to the Council for review. If the Council approves, the report is considered by the Reference Committee and finally by the Board of Trustees I believe it is obvious that a very excellent review mechanism exists and that the Task Force, as well as the Council, is composed of highly qualified psychiatrists who are thoroughly familiar with the scientific method and are capable of evaluating published literature. I hope this information is of value to you

Sincerely yours,
Ewald W Busse, M D
President

EWB:bsk
cc: Drs Garber and Barton
SECTION IX—References


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New advances in medicine are followed by a gathering of the information in scientific journals and books. The new journals arise because standard medical journals refuse to accept papers which appear critical of the standard approach. The new books arise in response to public demand. The presence of the new literature stimulates interest among physicians and other professional workers who in turn contribute to it. This is happening in the field of orthomolecular psychiatry. There is a large body of literature available. Most of it is listed here for the convenience of everyone, lay person and professional. Every book contributes directly or indirectly to the theory or practice of orthomolecular psychiatry.


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SUMMARY

We have examined critically and carefully the APA Task Force Report on megavitamins and orthomolecular psychiatry. We concluded that the report was biased, unfair, and contained a large number of major and minor errors. A study of the composition of the committee and the way it behaved explained why it carried out its mandate the way it did.

The chairman clearly voiced his bias and antagonism in a public presentation given several years before it is likely he was influential in selecting other members of his committee. This included one of his junior professors who would unlikely see things differently from his chairman, two from NIMH then well known for its antagonism toward our work, and one man just preparing himself to launch a series of critical assaults based upon experiments we consider inadequate. He made no attempt to repeat in any scientific way any of our early controlled experiments.

Not only was the committee clearly biased, it conducted its affairs in such a way as to avoid that degree of objectivity essential for any proper investigations. The committee not only should have been fair, it should have appeared to have been fair. Objectivity could have been insured by having orthomolecular representatives on the board and by inviting orthomolecular psychiatrists to present their data. This was not done, nor did the committee conduct any clinical experiments.

The report is characterized by the following:
1. Pronounced bias against orthomolecular psychiatry
   a. By a selective examination of the published reports. In any corroborating paper the positive conclusions were played down and minimized and possible side effects and toxicity were exaggerated. In every negative paper the positive or beneficial effects in these reports were minimized, played down, or ignored while negative findings, no matter how insignificant, were exaggerated.
   b. By the use of adjectives designed to support the preconceived bias of the committee.
2. By distorting our conclusions:
   a. By ripping phrases out of sentences which changed the meaning, and
   b. By misreading simple tables and statistical data.

Support for these charges is provided by a careful examination of all the published reports with the way the committee abstracted them. Our reports are listed and briefly summarized in the appendix. This is followed by a brief abstract of all the corroborative reports, most of them missed by the committee. We would have given equal emphasis to any negative report where a serious attempt was made to repeat any of our work. We have not been able to find one.

Finally, we have reprinted Dr. L. Pauling's critique of the APA Task Force Report and his rebuttal of the three letters attacking his position.

Since the committee accepted only evidence from double blinds (even if they were not) completed by others, we have presented a discussion of the theoretical and practical aspects of the double blind methodology. We were the first psychiatrists to use the double blind and among the first to realize its serious limitations as a method for testing efficacy of treatment.

Double-blind methodology is under attack by cancer research scientists. Recently Dr. C. Freireich, Director of Developmental Therapeutics at M.D. Anderson Hospital and Tumor Center in Houston concluded that the limitations of such trials are so serious that there are few, if any, indications for using the classical clinical trial strategy for evaluating and discovering new treatments for cancer. Other types of controlled studies in clinical research are superior, he concluded. National study groups foster consensus-type research which stifles the creative individual with the capacity for innovative work. It is obvious that scientists are beginning to question...
seriously double-blind experiments

We finally concluded that the actions of the American Psychiatric Association and its subcommittee are explainable only if one took into account the spirit of Watergate then rampant in Washington, among some of the government agencies and the American Psychiatric Association, headquartered in Washington
SECTION XI—REAL Attempts to Corroborate with Failure to Confirm Original Studies

We have been unable to find a single published study. The negative studies referred to by the APA Task Force made no attempt to replicate any of the original double-blind studies. They made no attempt to use comparable patients, to use the same treatment protocol, or to use the same criteria of improvement in hospital or after discharge. Lehmann (1976) admits this, but then complains that the treatment has changed. Not even our first two double-blind experiments were replicated. His argument would be much more persuasive if he, or anyone else, had duplicated our first controlled experiments.

Suppose our first double blinks were duplicated with careful attention to our published procedures, but the results were negative. If then we had argued that we had now changed (improved) the treatment procedure so that the attempt to corroborate was invalid, then we could have been accused of slipping out of the debate. But this has never happened. Lehmann's argument really cannot be taken very seriously until our original experiments are repeated. We cannot analyze why no attempts to duplicate have been made. It is as Joyce has written:

"To explore the reasons why some people choose a design for their experiments that is almost bound to lead to negative results is a little outside our brief."

There is no bibliography of negative reports with respect to orthomolecular psychiatry.
ADDENDUM

A Memo Received from H, Osmond After Completion of This Report

Psychiatric News, July 2, 1976, carried a report of an open meeting held by an APA Task Force on Electroconvulsive Therapy. It was called to hear the views of APA members in order to guide the Task Force in drafting a report to APA. Dozens of members spoke in a total of six hours of hearings. The Task Force also invited comments from APA members who did not appear at the meeting.

It appears from this that the APA can possess no general instructions for the conduct of its Task Forces. Nothing could be less alike than the behavior of those running the ECT Task Force and those examining megavitamins. Just why this should be is anyone's guess, but it is a striking bit of evidence that the Megavitamin Task Force was conducted differently from at least one other Task Force. The procedure, that of an open hearing at which those who support and those who oppose the particular treatment give their views and can be questioned, seems a considerable improvement upon the practices of that other Task Force. As it turned out the opponents of ECT either did not turn up, or there are far fewer of them than we have been led to believe.

It is interesting that the discussants dealt with two problems which preoccupied the Task Force:

(1) No one knows why ECT works
(2) The data base for ECT, after nearly 40 years, is not all that it might be.

This is one of the well-known differences between Clinidok and the combination of Superdok and Megadok. It is also of interest that the question of the efficacy of psychotherapy comes up once again. It seems that the evidence in favor of megavitamins is a great deal more than for psychotherapy and apparently ECT if this account is correct. Oddly enough Lothar Kalinowsky, who was present for most of the session, which lasted six hours, did not partici-