Letters to the Editor

A Corrective Response to the Note of Criticism Concerning the Double-Blind Study of Niacin Supplement in the Treatment of Schizophrenia

To the Editor:

It has recently come to our attention that Dr. De Liz has published "A Note of Criticism Concerning Wittenborn's Paper on an Experimental Double-Blind Research Design Dealing with the Action of Nicotinic Acid on Schizophrenia" (1973) reprinted (The Blind Double-Blind Studies, CSF). Since his note is based on errors of fact and interpretation, we wish to offer corrective rejoinder for the interest of those who may have been concerned about the explicit and implicit inconsistencies between our original report (Wittenborn et al., 1973) and Dr. De Liz's note of criticism.

Dr. De Liz erroneously identifies himself as Senior Psychiatrist for the niacin project. E. S. Paul Weber, M.D., Diplomate in Psychiatry, was appointed to the Rutgers Interdisciplinary Research Center as Research Specialist in Psychiatry for a period which included the course of the niacin study. Dr. Weber was the responsible psychiatric collaborator for the niacin study. Dr. De Liz was a full-time member of the medical staff of the New Jersey State Hospital at Marlboro, assigned to the County Cottage where the niacin patients were housed after their admission. He left the hospital while the project was in its second year. During the early part of the inquiry, Dr. De Liz provided many symptom ratings on a paid part-time basis. In the niacin study, symptom-rating scales were used independently by a physician, by a senior nurse, and by a psychologist. The analysis of symptom-rating data was based on a composite of these three independent ratings (Wittenborn et al., 1973). The diagnostic disposition and final selection of each patient was the responsibility of Dr. Weber.

The patients were assigned to high-dosage niacin and control treatment on a 60-40 ratio, not 50-50 as Dr. De Liz states. The control patients received low-dosage niacin (6 mg daily), not a placebo as Dr. De Liz states. Dr. De Liz states that he suspected a break in the double-blind code. The medication was dispensed by the hospital pharmacist, and he was the only person who had access to the treatment code. The pharmacist understood the necessity for protecting the code. When the question of the integrity of the code was raised, the Project Director reviewed the security of the code with the hospital pharmacist and advised him that a member of the staff suspected that it had been broken. The pharmacist provided assurance that treatment information had not been and would not be given to anyone without the Director's authority.

Dr. De Liz correctly states that the assessment procedure made no provision for "deeper apperceptions." The requirements of the research plan and the manner in which they were pursued were specified in a formal protocol and followed closely on a daily basis. In addition to staff meetings, the integrative surveillance included daily review of data as they were submitted, several daily telephone calls, and frequent conferences with individual members of the data-gathering staff. Although there was consternation when some of the patients became pigmented, members of the staff performed their roles without regard to any private attitudes concerning niacin. The continuing staff was an effective team, and each member perceived the other members as functioning in a manner consistent with the requirements of the research protocol and mores of his respective profession.

When pigmentation first appeared among the patients, the treatment code for each pigmented patient was broken, and various precautionary, dermatolo-gical tests were conducted. Since most patients felt self-conscious about the pigmentation, and since the pigmentation was on parts of the body ordinarily covered by clothing, the individual's pigmentation was not generally known. Nevertheless, it would have been impossible to conceal the fact of pigmentation from the project medical and nursing personnel who examined the patients and unethical to deny its association with high-dosage niacin. The code was broken also for the very few patients who became significantly hyperglycemic. These patients were withdrawn from the study.

Dr. De Liz comments on eight or 10 pigmented patients during the course of the niacin research. Since his participation was limited, he was unaware that among the 47 patients completing 24 months on high-niacin medication there were 23 cases of pigmentation.

Regarding the pigmentation, Dr. De Liz states, ". . . no such skin reactions have been, to my knowledge, ever found in literally thousands of schizophrenics who were treated with massive amounts of that vitamin continuously during many years." Nevertheless, in correspondence with the Project Director such pigmentation had been described by Dr. Hoffer as a possible adrenochrome deposition (personal communication). This pigmentation has also been described in personal communication from a psychiatrist in a New Jersey private clinic. Such pigmentation in response to high-dosage niacin is well documented in the literature (Brown and Winkelmann, 1968; Parsons and Flinn, 1959; and Tromovitch et al., 1964).

Dr. De Liz states that at least one patient correctly surmised that he was not receiving high-dosage niacin and supplemented his regimen by using drugstore niacin. We came to know the patients and their home circumstances quite well. Any violations of the medical requirements of the protocol were noted, and patients who were not cooperative with the medication regimen had to be dropped for this reason. This factor of attrition did not distinguish between the treatment groups (Wittenborn et al., 1973).

Dr. De Liz assumed that if patients suspected that they were receiving "placebo" this would be communicated to other patients and would be reflected either in their progress or in the manner in which progress was assessed. Since most of the treatment was conducted on an outpatient basis, it seems unlikely that any such doubts were generally shared. Had there been a "massive disillusionment" among the control patients, this should have been reflected in the dropout rate, but there was no significant difference between the groups in rate of attrition. At the conclusion of the project, there were as many protests against the discontinuation of the project from the control group as from the high-niacin group.

In relation to the presumptive break in code, Dr. De Liz refers to a "massive alteration of their total personality . . ." Our data revealed no such contrasts

between the two treatment groups at any time, and the only massive alteration was the very substantial, continued improvement recorded for both the niacin and the control groups.

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REFERENCES

De LIZ, A. J: A Note of Criticism Concerning Wittenborn's Paper on an Experimental Double-Blind Research Design Dealing with the Action of Nicotinic Acid on Schizophrenia. J. Orthomolecular Psychiat. 2:115-117, 1973.

De LIZ. A. J.: A Note of Criticism Concerning Wittenborn's Paper on an Experimental Double-Blind Research Design Dealing with the Action of Nicotinic Acid on Schizophrenia. Reprinted in The Blind Double-Blind Studies, Canadian Schizophrenia Foundation. (Pamphlet not dated).

WITTENBORN, J. R., et al.: Niacin in the long-term treatment of schizophrenia. Arch, Gen. Psychiat. 28:308-315, 1973.

HOFFER, A.: Personal communication.

BROWN, J., and WINKELMANN, R. K.: Acanthosis nigricans: A study of 90 cases. Medicine 47:33-51, 1968.

PARSONS, W. B., Jr., and FLINN, J. H.: Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid. Arch. Intern. Med. 103:783-790, 1959.

TROMOVITCH, T. A., JACOBS, P. H., and KERN, S.: Acanthosis nigricans-like lesions from nicotinic acid. Arch. Dermatol. 89: 222-223, 1964.

Dr. De Liz's Rebuttal

To the Editor:

In Dr. Wittenborn's rebuttal of my article, "A Note of Criticism Concerning Wittenborn's Paper on an Experimental Double-Blind Research Design Dealing with the Action of Nicotinic Acid on Schizophrenia," he states: "Since his note (Dr. De Liz) is based on errors of fact and interpretation, we wish to offer corrective rejoinder for the interest of those who may have been concerned about the explicit and implicit inconsistencies between our original report and Dr. De Liz's note of criticism."

I would like to ask Dr. Wittenborn what the main premises are from which he may infer statements entailing authoritative corrective rejoinders relative to my anthropological, analytic interpretations of the transactions and transformations involved in a small group of people as a social structure. After scanning Dr. Wittenborn's history of published material, however, I could not find those premises. From this fact, the inevitable conclusion follows that Dr. Wittenborn cannot constructively apply his "magical yardstick" to evaluate the correctness or incorrectness of a piece of work of a structural analyst directly acquainted with the paradigms and strategies of research of Prof. Claude Levi Strauss, Chairman of Anthropology of the College of France.

I felt and reasonably so that I was carrying the greatest load of work. E. S. P. Weber, M.D., as reported to me by Dr. Wittenborn, was in charge of reviewing all the psychiatric ratings relative to the patients who had been continuously rated during one year. Dr. Wittenborn appears concerned in minimizing my work and my training by directly stressing that I was not a Diplomate in Psychiatry. It is, however, far from true that a Diplomate in Psychiatry is logically more knowledgeable than one who is not. If Dr. Wittenborn deliberately intended to imply that such a conclusion doesn't apply to any comparison between my professional competence and Dr. Weber's, he certainly appears to confuse psychology with logic. For the logical analysis of knowledge is solely concerned with the justification or validity of

propositions. It deals with the testability or non-testability of statements. It is concerned as to whether or not certain statements are or are not dependent on other statements, or whether they contradict each other. It appears clear that Dr. Wittenborn failed to distinguish logically between his psychological processes relative to his idea that I was professionally inferior to Dr. Weber and the methods and results of examining the ensemble of his propositions relative to this matter.

I did not ask Dr. Wittenborn to be his collaborator. It was he who pleaded with me to accept the position. Before accepting me, Dr. Wittenborn found out that my training in psychiatry had been obtained in one of the finest Centers of this country - Psychiatric Training Faculty of Massachusetts, with its wealth of learning centers and hospitals associated, as it was, with the Harvard Medical School, Boston Medical School, Tufts Medical College, Boston Psychoanalytic Institute, and the Institute of Biological Research in Schizophrenia, headed by Prof. Pincus. Dr. Wittenborn knew also not only that I had worked many years as a field worker in Africa, but that I had received a Ph.D. in Anthropology of Columbia University in 1953.

Dr. Wittenborn knew also that I was one of the five anthropologists in the world who, in 1947, received a post-doctorate fellowship by the internationally known Dr. Wenner-Gren Foundation for Anthropological Research, New York City, N.Y. Finally, he had read my paper on a double-blind research project concerning the pharmacological properties of a monoamine oxidase inhibitor — iproniazide —published in conjunction with Dr. Harry Freeman, at the time Director of Research of Worcester State Hospital and Professor of Psychiatry of the Boston Medical School. An abstract of this paper was published in the Journal of the A.P.A. in 1958 and in the **Journal of Nervous Diseases** in the same year.

This was a pioneer paper because its results helped eliminate that mood-elevator drug from therapy of psychotic depressions in favor of some other less toxic drugs belonging to the same pharmacological category.

Dr. Wittenborn knew very well that during the first three months of the project only 18 - 20 patients had been collected by the psychiatrist in charge, Dr. Keremitzi, who was at the time Director of Research at Marlboro State Hospital. In all fairness, it should be said that Dr. Keremitzi's alleged slow progress was absolutely justified given the well-known difficulties involved in making accurate diagnosis of schizophrenia. During Dr. Keremitzi's absence abroad, he was fired and replaced by me. My job was of tremendous complexity for I had to select 100 patients as soon as possible

as the pressures of the National Institute of Mental Health in Washington were becoming very strong and were demanding a faster pace in our work. Meanwhile, E. S. P. Weber had temporarily left the project and told me that he was planning to go to North Africa. Dr. Wittenborn knows exceedingly well that I did collect 100 patients myself and incidentally, I even included my gardener of my house in Plainfield, N.J. Without my effort in getting the patients, the whole research project would not have gotten off the ground.

But let's go to the main point! Dr. Wittenborn appears without a minimum degree of reluctance to minimize the well-known fact that the double-blind code had been broken. I completely repudiate Dr. Wittenborn's contention that, although certain patients failed to adhere to their sick role by breaking the code, they have all been dismissed from the project. I know for sure that several did remain at least two years. It is also not true, contrary to Dr. Wittenborn's assertion, that the patients who broke the code were dropped, or that they had very little chance to communicate their discovery to others as they were being seen in an outpatient clinic after discharge from the hospital. On the contrary, the patients had plenty of time to tell their story while waiting for the

Diplomate Psychiatrist when they gathered for two hours in the waiting room, an occurrence which was quite common. It even happened several times that the nurse, Mrs. Brown, called me to replace Dr. Weber, because the patients had been waiting for hours and the Diplomate Psychiatrist didn't come.

I find it also curious that his article is signed by nine Ph.D.'s when, at the time, most of them were still graduate students in psychology, while Mary Brown who signs with a M.S. was at the time the nurse in charge.

In his original paper, Dr. Wittenborn claims that the sample of patients consisted of 100 schizophrenic patients. However, in his second paper he states that the percentage of patients whom he conclusively found to have made more progress both clinically and in terms of social adjustment under the influence of nicotinic acid as compared to similar samples of patients who had received placebos were not schizophrenics**.** From this statement, Dr. Wittenborn hastens to conclude that nicotinic acid really failed to help schizophrenic patients over and above those who were maintained on neuroleptics and placebos. His final advice is that at this stage of research the therapeutic use of nicotinic acid in schizophrenia is not clinically justified.

In all fairness, Dr. Wittenborn left the door open for further research in this complex field.

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Congratulations to Editors

To the Editor:

My reason for writing is to congratulate the editors for a most excellent issue of Orthomolecular Psychiatry - Volume 4, Number 3, 1975. All the articles were well researched, well written, and provocative. This issue could hold it over any publication now extant in the field of medicine. Even psychiatrists would have a difficult time finding fault with this issue.

Peat's article on biochemistry and the brain answers questions for the Orthomolecular physician and will provide those new to the field with a firm foundation. Dr. De Liz's article proves a point beyond a shadow of doubt. Dr. Osmond is his usual searching and engaging self. He throws out a challenge to treat psychiatric patients as sick people! This is something we do - and which most psychiatrists should do. This single short article could change the whole field of human relationships if we all worked toward that goal.

One can give favorable mention to each and every article in the quarterly - a most unusual event for any publication in any field of endeavor.

Are there copies available for distribution to others?

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