

data are available to answer these questions, and, thus, to allow more rational, effective, and economical delivery of limited treatment resources.

The *Bulletin* invites readers to share their views on this most difficult issue. Of special interest are innovative programs in which both somatic and nonsomatic approaches to treatment are prominent. Also welcome are comments

on other issues relevant to schizophrenia or on the articles published in this and previous *Bulletins*. Remarks should be addressed to:

At Issue
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nicotinic acid in the treatment of schizophrenia: a summary report

In response to the "At Issue" column in the Fall 1970 Bulletin, Drs. Thomas A. Ban and Heinz E. Lehmann have offered for publication a summary of their first progress report of the Canadian Mental Health Association's Collaborative Study, "Nicotinic Acid in the Treatment of Schizophrenias." The complete report** was published as a monograph by the Association, which has graciously released the summary that appears below.—The Editors.*

The hypothesis that schizophrenia is the outcome of stress-induced anxiety and a specific failure of metabolism which results in adrenochrome, a psychotoxic oxidation product of epinephrine, was formulated by Hoffer, Osmond, and Smythies (3). In the absence of specific drugs which interfere with adrenochrome formation, the administration of nicotinic acid was proposed to prevent excessive epinephrine production under stress, thus restricting the supply of the substance from which the psychotoxic aminochrome is formed.

Following the first clinical trials, Hoffer's group (4) suggested that high (at least 3,000 mg./day) dosages of nicotinic acid have a beneficial effect

in schizophrenic patients and have virtually no toxicity; subsequently, a controversy arose regarding the effectiveness of nicotinic acid treatment. Because schizophrenia is one of the major Canadian public health problems, a collaborative study was initiated by the Canadian Mental Health Association (CMHA) in December 1966 to examine the usefulness of nicotinic acid in the treatment of schizophrenic patients.

The CMHA Collaborative Study began 3½ years ago, and all that can be said on the basis of findings to date is that available evidence strongly suggests that nicotinic acid or nicotinamide is not the treatment of choice for all schizophrenic patients, under all possible conditions, and without any further considerations. In one of the completed studies, the addition of nicotinic acid or nicotinamide to the regular, freely administered phenothiazine treatment regime for a period of 6 months did not have any measurable therapeutic effect in a group of newly admitted schizophrenic patients. Moreover, patients in the placebo group received a lower total and lower average daily amount of phenothiazine drugs than those on either of the active substances (analysis of variance, $p < 0.05$). The placebo group was also hospitalized for a lesser number of days, although this did not reach statistical significance. By contrast, partial data from another study revealed that the mean daily dosage of chlorpromazine required during first hospitalization in an acute (or subacute) schizophrenic

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group was lower in both the nicotinic acid- and nicotinamide-treated patients than in the placebo group. It was noted, however, that the lower average daily dosages of chlorpromazine were accompanied by a considerably longer period of first hospitalization than was required for the placebo group.

Systematic attempts to identify a group responsive to nicotinic acid revealed that, in the dosage used, it has an effect on the internal inhibitory process activity of chronic schizophrenic patients (7). Considering the fact that in some of our more recent studies we have seen a heterogeneity within the chronic schizophrenic population and, indeed, a shift in the direction of inhibitory process activity in those patients who could be maintained without antipsychotic medication over a 12-month period, one may speculate that it is this chronic schizophrenic group which might benefit from nicotinic acid treatment.

For some time the adrenochrome theory of schizophrenia was the only rational basis for nicotinic acid treatment, but in the light of more recent scientific information other hypotheses on the nature of schizophrenia and the action mechanism of nicotinic acid were formulated. In the transmethylation hypothesis of schizophrenia, Kety (6) suggested that the disorder of the methylation process is primarily responsible for the functional changes at both the neuronal and behavioral levels. The same disorder may also lead to the production of abnormally methylated compounds. If one considers that transmethylation is an all-encompassing process, it seems reasonable to suggest that the disturbance of this process might produce such diverse, fundamental, and all-embracing changes as are encountered in schizophrenic patients.

The active methyl donor involved in the transmethylation of amines is S-adenosylmethionine (SAME). In recent experiments, Baldessarini (1) found an increase of SAME levels in the central nervous system after methionine loading but a depletion of the brain concentrations of SAME after the administration of monoamine oxidase (MAO) inhibitors. These observations correspond with clinical findings that schizophrenic patients, given methyl donors and a MAO inhibitor, suffered a striking exacerbation of psychosis. Furthermore, they support the speculation

that transmethylation could be facilitated by such simple means as increasing the availability of the methyl donor by methionine loading and that transmethylation could be prevented or interfered with by such simple means as nicotinic acid administration. This hypothesis has been tested in one of the CMHA Collaborative Studies. It was found that prior and simultaneous administration of nicotinic acid in a fixed dosage (3,000 mg./day) could not prevent the exacerbation of artificially induced psychopathology in chronic schizophrenic patients; nor could nicotinic acid counteract the artificially exacerbated psychopathological changes. The same dosage of nicotinic acid (3,000 mg./day) was, however, sufficient to produce a statistically significant ($p < 0.02$) improvement within 2 weeks at the initial stage of this study (i.e., prior to the commencement of methionine and tranylcypromine administration). In view of this, it is reasonable to speculate that the amount of nicotinic acid—the same dosage was maintained during and after methionine and tranylcypromine administration—was possibly insufficient to handle the induced biochemical changes and that administration of larger doses of nicotinic acid might have provided valuable information.

Despite the accumulating information on the role of transmethylation processes in schizophrenic psychopathology, there are no indications that the clinical use of nicotinic acid in the treatment of schizophrenic patients has increased. This clinical reserve may be due to the controversial findings in "controlled" studies in which statistical methods were employed on nosologically, but not necessarily biochemically, homogeneous groups. The findings that have accumulated during the new psychopharmacological era strongly suggest, however, that there are numerous schizophrenias (i.e., conditions utilizing the same final behavioral pathways), but that the abnormality of methylation processes, which might be alleviated by nicotinic acid treatment, is associated with only one or a few of these disorders.

The first successful attempt to identify patients on the basis of abnormality of methylation was made by Buscaino, Spadetta, and Carella (2). This was followed by the application of a more direct *in vivo* approach, employing radio-

active isotope techniques, by Israelstam, Johnson, and Winchell (5). The latter method was modified for *in vitro* assessments by Tran,¹ who suggested this modification become part of the CMHA Collaborative Study. The application of the new technique in the selection of patients would enable us to carry out the first experiment in our series of studies in which statistical methods could be employed meaningfully.

In view of the controversial clinical findings and in the absence of verified indicators of therapeutic responsiveness, the practical decision of whether to prescribe nicotinic acid should be influenced by consideration of its known adverse effects. It is important to realize that nicotinic acid is a highly potent substance, which has a profound effect on several metabolic systems; e.g., oxidation/reduction and transmethylation. Even more importantly, there is sufficient evidence to warrant special caution if nicotinic acid is to be prescribed for patients suffering from diabetes mellitus, gout, duodenal ulcer, or liver disease. As seen in the CMHA Collaborative Study, dermatological, gastrointestinal, hepatic, and cardiovascular reactions are rather commonly associated with high dosage nicotinic acid administration.

At the same time, it must be remembered that schizophrenia is a severely debilitating disease which disables a considerable percentage of the general population. Therefore, to withhold or deny, whether on the basis of empirical findings, medical thinking, or statistical probabilities, any treatment which holds some promise—even if no scientific evidence has as yet been provided for its usefulness—may, at this stage of development, be contrary to the physician's art.

The finding that the substance which causes the peculiar odor in the sweat of schizophrenic patients is the result of transmethylation and that the smell in the dormitory of schizophrenic patients is not necessarily the consequence of poor social environment in the hospital ward again emphasizes the importance of disciplined, clinical observations and rigorous medical thinking when dealing with psychiatric patients. It has been 18 years since the first patients were

successfully treated with high dosage nicotinic acid administration. The clinical information which has accumulated during this period compares unfavorably to the scientific progress made in this area of research. More and more, a need makes itself felt—a need to develop a new medical language of psychiatry designed to aid in the integration of new scientific discoveries into the clinical treatment of schizophrenic patients.

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¹Personal communication from Tran.

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