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Correspondence

NICOTINAMIDE ADENINE DINUCLEOTIDE IN THE TREATMENT OF CHRONIC SCHIZOPHRENIC PATIENTS

DEAR SIR,

The paper by Kline *et al.* in the July, 1967, issue of the *Journal* (113, 731–742) calls for some comment. The information contained in it has been widely circulated in the United States, both by press conferences and in some very misleading statements in the *Newsletter* of the American Psychiatric Association for April, 1967. This reports a failure to confirm work published earlier by one of us (A.H.) in 1966 and by both of us in 1966.

In our opinion this study shows how easily a double-blind methodology can create a false sense of security in competent investigators, who by concentrating their attention on one particular aspect of the experiment did not attend to equally important matters such as using the same therapeutic material upon similar patients. While undoubtedly using a more refined experimental design, the Kline study, from its own account, used NAD, whose preparation and activity is questionable, on a small group of chronic, very deteriorated patients from Rockland State Hospitals, who sound far more ill than most patients from good psychiatric hospitals today. Indeed, one of the authors (Dr. J. Cole) informed one of us privately that he wondered whether some of the patients might not have been brain-damaged. According to the Kline paper, their NAD was reported as 70 per cent. active. This was placed in enteric capsules in their own laboratory. The Kline *et al.* doses therefore ranged from 0·7 gr. to 1·4 gr. per day, whereas in our study we used 1 to 2 gr. It appears that when placed in gastric juice these capsules disintegrated. Several of their patients were flushed after taking the capsules, and since pure NAD does not produce a flush when given orally in enteric-coated capsules, this strongly suggests the presence of free nicotinic acid. It is, therefore, unlikely that very much of the 70 per cent. NAD arrived intact in the blood. Pfeiffer (1967) reported that he had compared the Kline capsules against NAD he had obtained and placed in double gelatin capsules, and also against the enteric-coated NAD which we used. He then compared these three preparations, using the quantitative EEG on normal volunteers in a double blind experiment. This showed that our NAD which we had used had the greatest activity, followed by Pfeiffer's own preparation Kline's preparation came last and showed very little activity at all. The statement then that "there is also the possibility that our DPN was not active or that the preparation was inadequate" seems to have been something of an understatement. It appears to us to be unnecessary to go to the trouble of reporting double-blind control studies in which a placebo is used against material which the authors concede might well be inactive, and which the evidence suggests probably was.

All Kline's patients (of whom only 10 out of 20 were on NAD) were residing in hospital, which according to his own work (Vestergaard, Abbott, Kline and Stanley, 1958) has a very high rate of amoebic intestinal infection.* Most of our patients were also chronic, but they had not spent years and decades residing in a hospital where infections of this kind are rife. Out of our original pilot group of 17, only one was comparable to this very chronic group which Kline *et al.* used. She had been in the Saskatchewan Hospital, Weyburn, for over 30 years without any evidence of remission. She had not responded to any medication, but had become very toxic on tranquillizers and had developed the purple pigmentation described by Greiner *et al.* (1964, 1965). This was treated at the Saskatchewan Hospital, Weyburn, by penicillamine. She had been on Mega Vitamin doses of nicotinic acid and ascorbic acid for many months. She was then transferred to the University Hospital. Here she was given NAD, and after four weeks was well enough to be discharged. Her psychiatrist from Weyburn, the hospital which sent her to the University Hospital, stated that had he not known her at Weyburn for two years he would not have believed that she had been schizophrenic (Hoffer and Osmond, 1966). At that time our supplies of NAD were running out

* A number of chronic patients were selected for physical fitness and freedom from disease and transferred to the research ward. Half had amoebic infection. The authors stated they were representative chronically ill schizophrenics in their hospital and concluded that such persons should not be included in scientific studies. Since infection with amoeba can cause chronic inflammation of bowel, this could prevent proper absorption of essential vitamins. In any event, a new variable is introduced, which Kline *et al.* simply ignore in their NAD study.

and no more was available. When she was examined several days later, the psychiatrist did not know that she was no longer having it. That afternoon she hit a nurse. She remained fairly stable for a while and was discharged to a private nursing home; but within two weeks her hallucinations and delusions recurred, and after a serious attempt at suicide she was re-admitted. For the next three months, an intensive effort at the University Hospital was made to bring her out of her psychosis, but everything failed and she was returned to Weyburn in the same condition that she had been on discharge from that hospital to the University Hospital. One could, of course, consider that this was a coincidence, but it would be a very strange one, for after 32 years of continuous hospital care she recovered only during the last two weeks of NAD and relapsed a few weeks after no more was available.

In our series several other chronics did not respond. Fourteen were tested with the HOD test (Kelm, Hoffer and Osmond, 1968) before, during and after NAD therapy. The mean Total Scores for those who were tested were 101 before treatment, 42 at their best during treatment, and 116 after treatment was stopped, when the NAD supplies had run out. When the scores showed a mean of 42, the patients were very much improved clinically, if not well. Unfortunately, the supplies of NAD were not available for a long trial, and it is impossible to know how long they would have remained well. They all relapsed a few days after NAD was stopped.

Several months ago an additional supply of NAD was obtained. One of the patients who had responded quickly to NAD in 1966 had relapsed after NAD was no longer available and remained chronically ill; she failed to respond to every treatment, including two series of ECT, tranquillizers, niacin, ascorbic acid and other chemotherapeutic measures. She was given 1½ gr. of NAD per day and within a few days became nearly normal. Two psychiatrists examined her independently and found her well. Over a two-year period of treatment she had never had normal HOD scores on two successive tests except for a month on NAD early in 1966. Her Depression Score varied between 10 and 18, her Perceptual Score from 6 to 22, her Paranoid Score from 1 to 9 and her Total Score from 50 to over 150. After two and four days on NAD in December, 1967, her HOD scores became normal. The scores are shown below.

Days on NAD	Depression	Perception	Paranoid	Total
2	5	7	1	29
4	1	1	0	6

She has remained free of her psychosis while being maintained on 1½ gr. per day.

It appears to us that the only conclusion one can draw from Kline's studies is that deteriorated NAD, which has been improperly prepared, does not help chronic, severely deteriorated male mental hospital patients. However, if one examines Kline's data, there is evidence that, contrary to his conclusion, some may have been helped. Only eight out of 20 of his chronic patients were able to complete the HOD test. In Saskatchewan, using the same test, out of over 500 chronic cases only 5 per cent. have been too ill to complete the HOD test. Of those eight who took the test, half received placebo and half the deteriorated NAD.

Table VIII from the paper by Kline *et al.* may be summarized as follows:

	Mean Scores on NAD	
	Before	After
Paranoid	5.8	3.3
Perception	14.0	6.5
Total	63.0	40.0

	Mean Scores on Placebo	
	Before	After
Paranoid	4.5	4.5
Perception	14.5	15.5
Total	65.0	66.0

All the changes in mean score on NAD are significant. Three of the NAD subjects showed significant decreases compared to one of his placebo group. Kline *et al.* report that two on placebo improved, but a decrease in total score from 23 to 19 is a random change and of no significance whatever (Kelm, Hoffer and Osmond, 1968).

The Gallant *et al.* study (1966) is a much better research, since only one variable was not replicated. Gallant's work suggests that NAD, known to be quickly active in non-deteriorated schizophrenics, is not active in chronic deteriorated cases. Recently evidence has arisen which suggests strongly that different batches of NAD made by the same company have varied in potency. The NAD must be prepared in special capsules which do not disintegrate until they have cleared the proximal part of the small intestine. Over six months ago, a supply of 1,000 gr. of crystalline NAD was sent to a reputable and experi-

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enced firm. They agreed to put it in enteric capsules, but they reported having run into various difficulties and it was prepared only recently.

Debates and difference of opinion between research workers are invigorating, but hastily conceived enquiries based on a particular kind of design are liable to be misleading, and an important matter of this kind can only be settled when ample quantities of properly prepared material of known efficacy can be made available for general use. Unhappily, that situation does not yet obtain. Indeed, believing that ample quantities of stable potent NAD would be provided, we ourselves had planned long before Kline to undertake a double-blind experiment on a considerably larger scale than his. Our initial report had to be made upon a small series of cases because for a number of reasons ample supplies of NAD and placebo were not available.

A. HOFFER.

800 Spadina Crescent East,
Saskatoon, Sask., Canada.

H. OSMOND.

New Jersey Neuro-Psychiatric Institute,
Box 1000, Princeton,
New Jersey 08540, U.S.A.

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BLOOD GROUPS IN PSYCHIATRIC ILLNESS

DEAR SIR,

A. B. Masters' recent article "The Distribution of Blood Groups in Psychiatric Illness" (*Journal*, November, 1967, p. 1309) is similar to one from our laboratory (Irvine and Miyashita, 1965). Readers may be interested in a comparison of results obtained by Masters in Lancashire with those obtained by us in Saskatchewan. The initial Saskatchewan work was based on 734 consecutive admissions to the Saskatchewan Hospital, North Battleford, a 1,100 bed public mental hospital serving a catchment area with a population of approximately 430,000. This preliminary work was primarily an attempt to replicate and possibly extend the findings of Lafferty, Knox and Malone (1957), and particularly those of Parker, Theilie and Spielberger (1961); this also seems to have been a primary aim of the work reported by Masters.

As we reported in 1965, our results tended to confirm the findings of Lafferty *et al.* and Parker *et al.*: Group A_1 tended to associate with schizophrenia; Group O with manic-depressive psychosis; Type E with neurotic-depressive reaction; and Kell with depressive diagnoses in general. In addition, we found a statistically significant positive association between involutional melancholia and blood Group O. Rather significantly, Masters further confirms Parker, Thielie and Spielberger's observation of an association between blood Group O and manic-depressive psychosis. The fact that such a relationship has been demonstrated in North Carolina, in Saskatchewan and in Lancashire strongly argues for its reality and pervasiveness, and hence for major research efforts to determine its mechanism and implications.

While our blind study tended to confirm all the expected trends based on Lafferty *et al.* and Parker *et al.*, there are several differences between Masters' findings and ours. Ultimately, this situation may be attributed to differences in diagnostic trends, and/or ethnic composition, between the Saskatchewan and the Lancashire studies. In any case, Masters' work did not confirm the associations between E-positivity and psychoneurotic depression, or between Kell-positivity and depression in general. Masters' failure to confirm a relationship between blood-type E and neurotic-depressive reaction is not surprising, since (1) this was the weakest trend in our cross-validational study of admissions, (2) we found no trace of such a relationship in a hospital-wide study of *in-patients*, and (3) a special study of depressives, undertaken in collaboration with Dr. G. Marjerrison, also failed to reveal such a trend. The failure of the Lancashire data to manifest the expected association between the Kell blood type and depression is more difficult to understand. Not only did our preliminary work show the expected trend among psychiatric admissions, but subsequent studies have revealed it among our hospital in-patients, and again in a group of concordantly diagnosed depressives (joint work with Dr. G. Marjerrison). Finally, we have demonstrated a statistically significant and specific positive association between the Kell blood-type and depression as