

Current Status of Chemotherapy of Schizophrenia

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NEUROLEPTIC TREATMENT

In the 18 years following the introduction of chlorpromazine in 1952 a large number of so-called neuroleptic drugs have been synthesized. By 1970, there were 10 chemical classes of compounds known which ameliorated schizophrenic symptoms; at least 50 neuroleptic drugs had been clinically investigated; and almost one half of those which had been studied were used in clinical practice (Table I).

Are Neuroleptics Effective?

However obvious it seems today, the superiority of therapeutically employed neuroleptics to placebo, i.e., the simple fact that neuroleptics are effective, had to be established and it took approximately eight years from the first psychiatric application of chlorpromazine to the establishment of definite evidence that these drugs do indeed have a therapeutic action (Cassey, et al.¹⁻²).

By now there has been abundant clinical evidence all over the world that neuroleptics are effective in the treatment of schizophrenic patients.

In their review on controlled studies Cole, Goldberg and Davies³ gave an account of a large number of psychoactive phenothiazines which were found to be more effective than placebo. Placebo equaled

Neuroleptics clinically used in the United States and/or Canada in the treatment of schizophrenias

<i>United States</i>	<i>Canada</i>	
<i>Phenothiazine Derivatives Aminoalkyls</i>		
Chlorpromazine	Thorazine	Largactil
Methotrimeprazine	Levoprome	Nozinan
Promazine	Sparine	Sparine
Trifluopromazine	Vesprin	Vesprin
<i>Piperazinylalkyl</i>		
Acetophenazine	Tindal	Notensil
Butaperazine	Repoise	Randolectil
Carphenazine	Probetazine	N.A.
Fluphenazine	Prolixin	Moditen
Perphenazine	Trilafon	Trilafon
Prochlorperazine	Compazine	Stemetil
Thiopropazate	Dartal	Dartal
Thiopropazine	N.A.	Majepitil
Trifluoperazine	Stelazine	Stelazine
<i>Piperidylalkyls</i>		
Mesoridazine	Serentil	Serentil
Piperacetazine	Quide	Quide
PropERICIAZINE	N.A.	Neuleptil
Thioridazine	Mellaril	Mellaril
<i>Thioxanthene Derivatives</i>		
Chlorprothixene	Taractan	Tarasan
Thiothixene	Navane	Navane
<i>Rauwolfia Alkaloids</i>		
Reserpine	Serpasil	Serpasil
<i>Batyrophenone Derivatives</i>		
Haloperidol	Haldol	Haldol

TABLE I

the active phenothiazine preparation in only 24 out of 95 studies, while in 71 it was definitely inferior to the various neuroleptics.

Is One Neuroleptic Better than the Other?

With the rapidly growing number of clinically used neuroleptics it becomes increasingly important that every new neuroleptic should have a better therapeutic index than chlorpromazine or any of the other clinically used neuroleptic drugs. Nevertheless, these therapeutic expectations have not been fulfilled.

In the already quoted article of Cole, Goldberg and Davies³ none of the reviewed studies showed any of the phenothiazine drugs to be superior in overall therapeutic efficacy to chlorpromazine—the first neuroleptic drug introduced—but in some of the studies promazine and mepazine were significantly less effective.

Similarly, there was no consistent evidence that any of the clinically used Rau-wolfia alkaloid, butyrophenone or thioxan-thene preparations were superior to chlorpromazine or to any of the other neuroleptic phenothiazines. On the other hand in some of the studies reserpine was found to be inferior in its therapeutic efficacy to chlorpromazine and also to fluphenazine and thioridazine.

While so far all effort to supersede the therapeutic effects of chlorpromazine have failed, there are indications that the newer neuroleptics may produce fewer adverse effects. A recent review in the *Medical Letter*⁴ lists 14 undesired reactions with various classes of neuroleptic drugs. Of these, 12 to 13 were encountered with phenothiazines, 10 with thioxanthenes and 8 with butyrophenones (Table II).

TABLE II
NATURE OF ADVERSE REACTIONS TO VARIOUS GROUPS OF NEUROLEPTICS
(*Medical Letter* 1970*)

	<i>Aminoalkyls</i>	<i>Phenanthri-az-ines</i> <i>Piper-azinyllalkyls</i>	<i>Piperidylalkyls</i>	<i>Butyrophenones</i>	<i>Thioxanthenes</i>
Oversedation	+++	—	+++	—	+++
Parkinson's syndrome	++	+++	++	+++	++
Akathisia	++	+++	++	+++	++
Dystonic reactions	++	+++	++	+++	++
Anticholinergic effects	+++	+++	+++	—	++
Postural hypotension	+++	+	+++	++	++
Inhibition of ejaculation	++	++	++	—	—
Lenticular pigmentation	+	+	—	—	—
Pigmentary retinopathy	—	—	++	—	—
Allergic skin reaction	++	+	—	+	+
Photosensitivity reaction	++	++	+4-	+	+
ECG abnormalities	+	+	++	—	—
Cholestatic jaundice	++	+	+	+	+
Blood dyscrasias	++	+	+	++	+

+++ = Frequent ++ = Occasional + = Rare

* ECG abnormalities were added to the adverse effects included in *Medical Letter*.

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Do Neuroleptics Differ in their Action?

The relatively limited decrease in toxicity, without a substantial increase in therapeutic efficacy, does not justify the large number of clinically available neuroleptics. Nevertheless, if the new neuroleptics would qualitatively differ in their therapeutic action from the older ones in general, or chlorpromazine in particular, this alone might justify their existence.

However disappointing it may be, all attempts to reveal differential clinical effects among neuroleptics fall short of verification to date. Similarly, all efforts of grouping schizophrenic patients on the basis of similarity of their response patterns to various neuroleptics have failed.

Independent of this there is the clinical observation that any particular patient may be therapeutically unaffected by a special neuroleptic agent, yet may respond to another neuroleptic drug. One possible explanation for this difference would be that different patients metabolize one or another neuroleptic differently. But studies in this direction have until now remained unrevealing.

DISCUSSION

In spite of all its limitations, however, the treatment of choice for schizophrenia today is pharmacotherapy with neuroleptics. According to Lehmann⁵ "no other single therapeutic procedure can compete with neuroleptic treatment in terms of rapid effectiveness, sustained action, general availability and ease of application." Furthermore, "it compares favourably with other therapies as far as incidence of side effects, complications and serious risks are concerned."

While the rate of spontaneous remissions from schizophrenia has been determined to be about 15 to 25%, modern pharmacotherapy had by 1963 resulted in a remission rate of between 50 to 60% for patients who had been ill for less than three years. Furthermore, discharge rate of 75 to 80% was claimed for all acute hospitalized patients within the

first year and for more than 50% within six months.

NIACIN THERAPY

But in spite of the reduction of hospital stay in the neuroleptic era, the percentage of "symptom free" schizophrenic patients has not grown by the introduction of neuroleptic drugs; the improvements have been confined to a shift from the prevalence of "psychotic" to the prevalence of "residual" symptoms (Kelly and Sargant⁶).

Accordingly, Vartanian⁷ in a recent publication discussed the "therapeutic pathomorphosis" of "terminal schizophrenia" and reported the release of productive symptoms after discontinuation of long-term drug therapy in 35 patients who were in advanced stages of schizophrenia. While prior to treatment it had been assumed that productive symptoms in these patients were irreversibly extinguished, he recognized that they had only been masked by the effects of neuroleptic drugs.

The recognition that neuroleptics are not curing schizophrenic patients has led to an increased interest in the testing of hypotheses based on biochemical theories in clinical psychopharmacological research. One of the first of these hypotheses was that schizophrenia is the outcome of stress-induced anxiety and a failure of metabolism which results in highly toxic mesca-line-like ("M") compounds.

Harley-Mason⁸ suggested that 3,4-dimethoxyphenylethylamine (DMPEA) may be the toxic agent responsible for the observed psychopathological changes (Fig. 1).

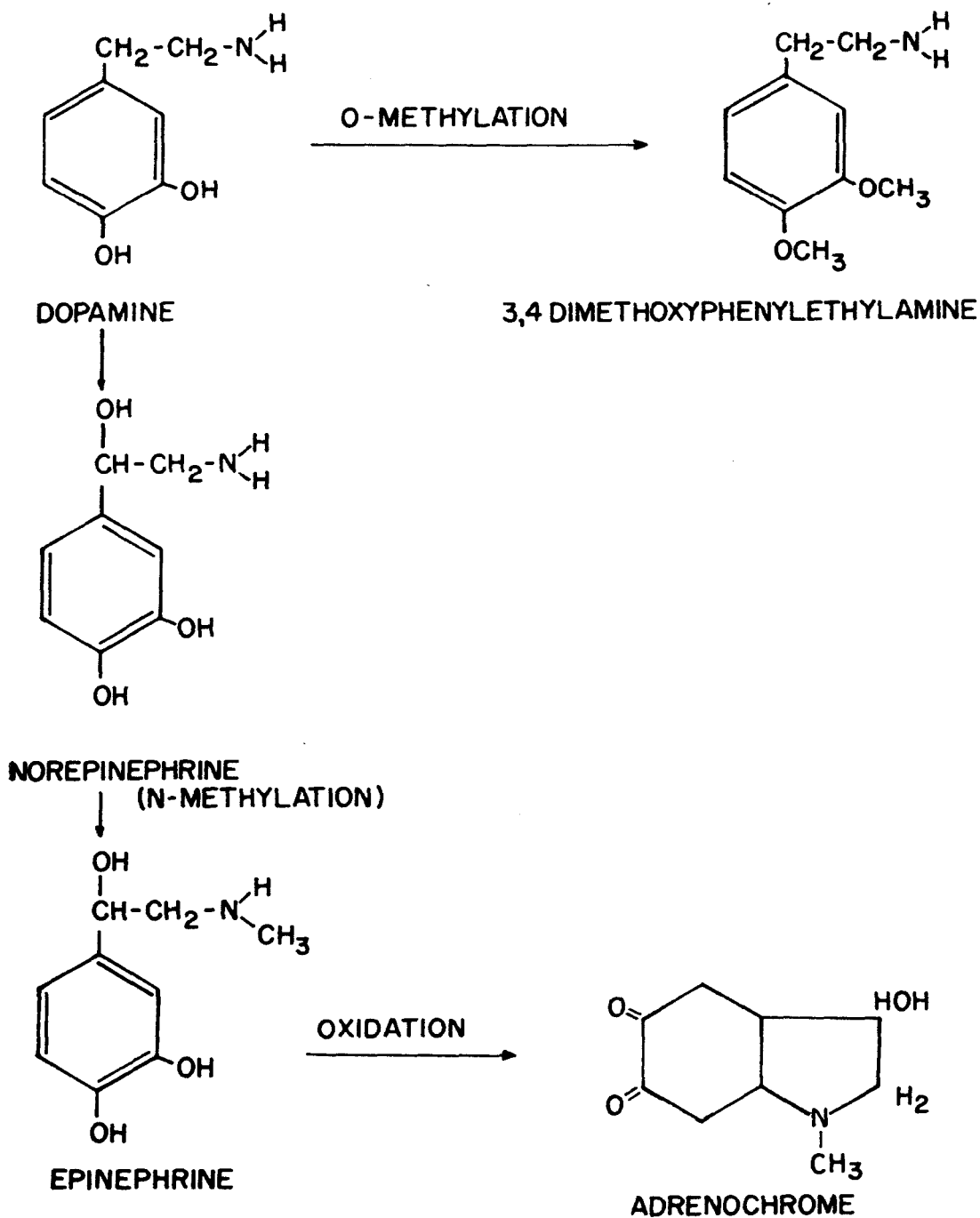
An alternative hypothesis proposed that adrenochrome, a psychotoxic oxidation product of epinephrine, was the "M" substance (Hoffer, Osmond and Smythies⁹). Its production was thought to be a result of the increased phenolase activity of

schizophrenic serum.

In the absence of specific drugs which interfere with adrenochrome formation, Hoffer, et al.,¹⁰ suggested that administration of nicotinic acid (which converts into

nicotinamide) to prevent excessive epinephrine production under stress, thus restricting the supply of the substance from which the alleged psychotoxic aminochrome is formed.

FIGURE 1



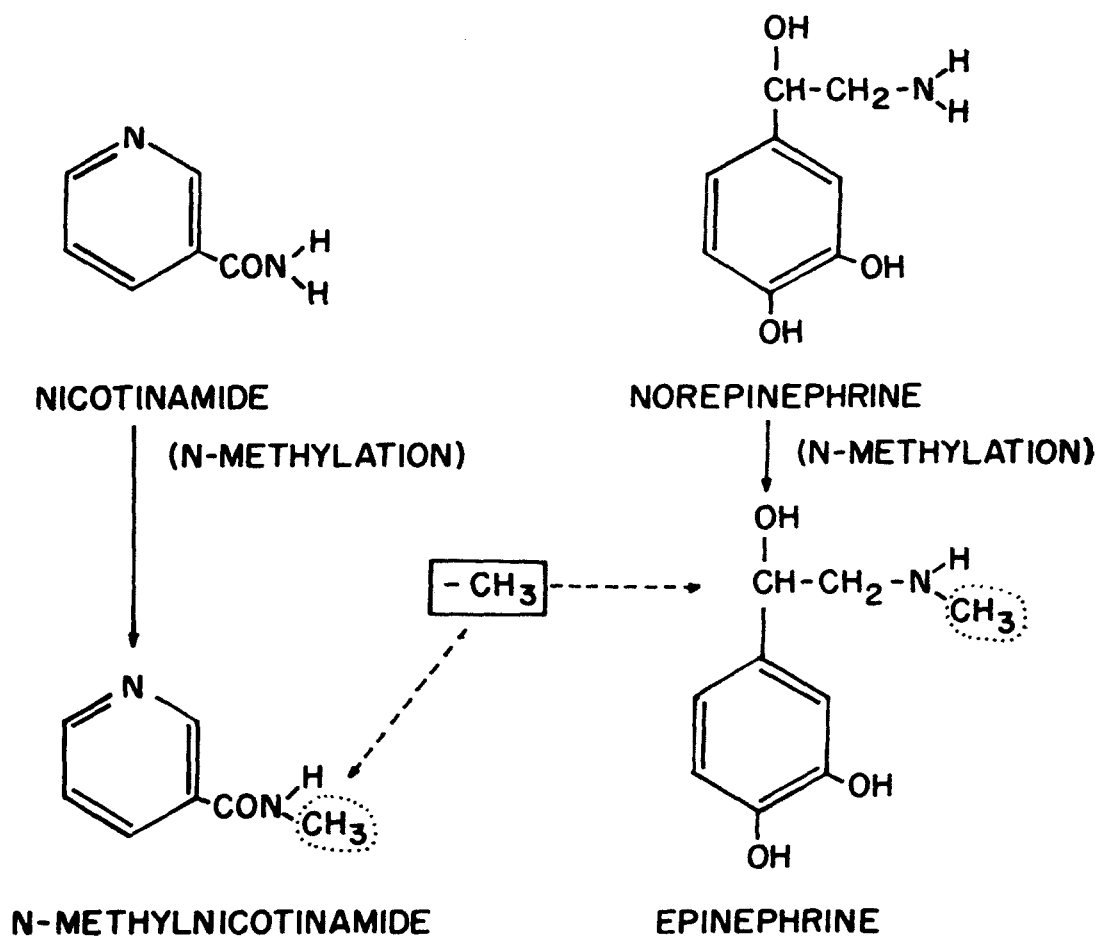
The formation of 3,4-dimethoxyphenylethylamine (DMPEA) from dopamine and the formation of adrenochrome from epinephrine.

The inhibition of epinephrine formation is thought to occur through the following mechanism: nicotinamide competes with norepinephrine for available methyl groups, which are mainly supplied in the diet by methionine, a sulfur containing amino acid, to form N-methylnicotinamide, one of its main metabolic end products (Fig. 2).

Following the first reports on successful clinical trials with nicotinic acid in schizo-

phrenic patients, a controversy arose regarding the actual therapeutic effectiveness of nicotinic acid, and because schizophrenia is one of the major Canadian public health problems the Board of Directors of the Canadian Mental Health Association (CMHA) decided about four years ago to set up a series of systematic studies which might lead to relevant information on the value of this treatment (Ban¹¹).

FIGURE 2



The formation of N-methylnicotinamide from nicotinamide and the formation of epinephrine from norepinephrine.

Results in the CMHA Collaborative Studies

Progress Report I

The first Progress Report on the CMHA Collaborative Studies was presented at the annual meeting of the Canadian Psychiatric Association in June, 1970 and was based on findings in the first two—out of a total of 12—clinical investigations (Ban and Lehmann¹²).

In one of these studies—a placebo-controlled clinical trial—it was demonstrated that the addition of nicotinic acid or nicotinamide to the regular—freely administered—phenothiazine treatment regime for a period of six months did not have any measurable therapeutic effect in a group of newly admitted schizophrenic patients.

Moreover, it was shown that patients in the placebo group received a lower total and a lower average daily amount of phenothiazine drugs than those on either of the active substances ($p < 0.05$).

Similarly, patients in the placebo group spent a shorter time in hospital than patients in the active treatment groups, although this did not reach the accepted level of statistical significance (Table III).

In the other study it was found that prior and simultaneous administration of nicotinic acid in a fixed dosage (3000 mg./day) could not prevent the exacerbation of artificially induced Psychopathology—by methionine loading associated with tranlycypromine administration—in chronic schizophrenic patients. Nor could nicotinic acid

chopathological changes.

However, it was also noted that the same dose of nicotinic acid—3000 mg./day—was sufficient to produce a statistically significant improvement ($p < 0.02$) within two weeks at the initial stage of this study, i.e., prior to the commencement of methionine and tranlycypromine administration.

In view of the controversial clinical findings and in the absence of verified clinical indicators of therapeutic responsiveness, Progress Report I concluded that "nicotinic acid or nicotinamide is not the treatment of choice for every schizophrenic patient, under all possible conditions and without any further considerations."

Furthermore, it was suggested that the practical decision whether nicotinic acid should be prescribed must be influenced by consideration of its known adverse effects. In this context it was pointed out that dermatological, gastrointestinal, hepatic and cardiovascular reactions were rather commonly associated with high-dosage nicotinic acid administration.

Interim Report I

Since Progress Report I, nine months have passed and during this period two further clinical studies have been completed and evaluated. The results of these were presented in Interim Report I at the annual meeting of the Research Committee of the Canadian Mental Health Association in March, 1971 (Ban¹³).

In one of these studies, a placebo-controlled clinical trial, it was demonstrated that during the two-year investigational period—regardless whether the patients were kept on the project or not—the average number of days spent in hospital was lowest in the placebo (211 days) and highest in the nicotinamide (353 days) treated group. Nevertheless, the number of days spent in hospital was only slightly higher (214 days) in the nicotinic acid than in the placebo treated patients.

TABLE III

Average phenothiazine dose per day (expressed in CPZ units) and average length of hospitalization in three treatment regimes

<i>Treatment Regime</i>	<i>Average Daily CPZ Units</i>	<i>Average Days of Hospitalization</i>
Nicotinic acid	730	90
Nicotinamide	705	88
Placebo	418	67

CPZ — Chlorpromazine

counteract the artificially exacerbated psy-



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Since the majority of newly admitted schizophrenic patients could not be sufficiently controlled with high dosages of nicotinic acid administration alone, the mean daily dosage of adjuvant chlorpromazine required during the investigational period was compared in the three treatment groups. It was found that the requirement was lower in both, the nicotinic acid (133 mg.) and the placebo (154 mg.) group than in the nicotinamide treated (180 mg.) patients.

In the other study, a placebo-controlled clinical trial, the hypothesis that the therapeutic efficacy of nicotinic acid is enhanced by the administration of Pyridoxine in chronically hospitalized schizophrenic patients over a one-year period was tested.

The rationale of this hypothesis is that Pyridoxine, via the opening of the kynure-nine pathway of tryptophan metabolism with the biological formation of nicotinic acid, reduces the formation of dimethylated psychotoxic indole metabolites.

Improvement—as expressed in total BPRS scores—reached the accepted level of statistical significance in the nicotinic acid ($p < 0.02$) and in the Pyridoxine group ($p < 0.001$), but not in the combined treatment group. However, no statistically significant difference was observed in the degree of improvement between the three groups.

On the basis of the first four completed clinical studies, Interim Report I concluded "that nicotinic acid therapy is not the optimal treatment for the average schizophrenic patient."

This statement was based on the results that

- (1) The overall therapeutic efficacy of nicotinic acid as the sole medication in newly admitted schizophrenic patients was not superior to the overall therapeutic efficacy of an inactive placebo.
- (2) That the overall therapeutic efficacy of nicotinic acid as an adjuvant medication in newly admitted schizophrenics was inferior to the overall therapeutic efficacy of an inactive placebo, i.e., nicotinic acid had a negative therapeutic effect.

DISCUSSION

Would these findings imply that nicotinic acid has no use whatsoever in the treatment of schizophrenic patients and that all further work in this area of research will remain in vain and should be terminated? The methodology employed in these studies did not and could not provide for such a categorical answer to this question.

As Psychopharmacology progressed, psychopharmacological work has become increasingly disciplined by inductive logic, which led to the utilization of the statistical method for the analysis of controlled studies in order to draw general conclusions on the basis of a limited experimental sample.

Needless to say, that the requirements of a controlled experiment are far from being fulfilled in clinical, psychopharmacological experimentation. Because of this, and probably even more so because of the absence of criteria for selecting truly homogeneous populations, all psychopharmacological studies, even those conducted under the best possible conditions, fail to give a rigorously valid estimation of experimental

error and fail to provide a genuine baseline for comparing the efficacy of the investigational substance with no treatment, a placebo, or a standard comparison drug.

But by the same reasoning, it would be erroneous to amplify the results of our clinical trials with other negative reports and— ignoring the positive therapeutic findings of Maslowski,¹⁴ Kassay and Pinter,¹⁵ Saarma and Vasar¹⁶ and Sehdev¹⁷—to conclude that nicotinic acid has definitely no place in the treatment of schizophrenic patients.

On the other hand, the fact remains that apart from pellagra and the encephalopathy of nicotinic acid deficiency, no other nicotinic acid responsive clinical Psychopathology has been successfully—and definitively—identified to date.

BIOCHEMICAL HOMOGENITY

In the absence of verified clinical indicators of therapeutic responsiveness to nicotinic acid in schizophrenic patients the recognition of biochemical heterogeneity within the schizophrenias becomes of crucial importance.

This biochemical heterogeneity was demonstrated—and correlated with clinical heterogeneity—in a series of experiments by Snezhnevsky and Vartanyan¹⁸ who studied the action of the serum of schizophrenic patients on the mitotic activity of cells in a particular culture (Hep-2).

At first approach, in comparing the quantity of mitotically dividing cells in cultures (in vitro), after their incubation with the serum of schizophrenic patients and with the serum of various control groups, they could not demonstrate any significant differences between them.

However, a detailed analysis revealed that the serum of schizophrenic patients with a continuous course of the disease possessed a marked antimitotic action. Conversely, the serum of schizophrenic patients with a periodic course stimulated the mitotic activity of all cell cultures.

Hence, the serum of schizophrenic patients with

the two polar types of development evoked opposite actions on the mitotic activity of cell cultures. Or, in other terms, the heterogeneous populations within the schizophrenias successfully covered up meaningful differences between schizophrenic patients and normal subjects.

Applying the same concept to the nicotinic acid problem, the crucial question remains the identification of biochemically homogeneous subgroups within the schizophrenic population for which the administration of a methyl acceptor substance would be useful.

Theoretical considerations led to the suggestion that the homogeneity of the schizophrenic population might be increased by the selection of schizophrenic patients on the basis of biochemical criteria, e.g.:

- (1) The presence of adrenochrome in the serum.
- (2) The presence of mauve factor.
- (3) Pink spot.
- (4) Bufotenin-like substance in the urine.
- (5) The presence of transmethylation disturbance.

One may speculate that groups identified on the basis of any one of these five criteria will be therapeutically responsive to nicotinic acid administration. But no consensus has been achieved in regard to adequate methods which can be clinically employed in the testing for biochemically homogeneous groups on the basis of any one of these five criteria.

Adrenochrome

Simultaneously with the controversial clinical findings some of the essential components of the adrenochrome hypothesis were questioned. Only in selected groups of schizophrenics (acute and aggressive) was it possible to demonstrate a definite increment of urinary catecholamine

excretion and the augmentation of oxidative processes remained, at best, a controversial issue.

That adrenochrome can be obtained by the treatment of epinephrine with various oxidants (in vitro) has been described long before the adrenochrome hypothesis was formulated (Green and Richter¹⁹).

On the other hand, the presence of adrenochrome (or adrenolutin) in the plasma of schizophrenics could not be verified by specific techniques. After a considerable dispute, however, the psychomimetic properties of adrenochrome were experimentally confirmed.

Although the presence of adrenochrome in human serum has never been demonstrated, Axelrod²⁰ succeeded in identifying the presence of a cyclizing enzyme in the human serum, capable of performing the specific transformation of epinephrine into the aminochrome. Nevertheless, the activity of this epinephrine cyclizing catalyst was found to be, instead of above the normal values, below the normal range (Altschule and Nayak²¹).

The consistently low values found in schizophrenics preclude the possibility of selecting a group of schizophrenics, for nicotinic acid treatment, in which the activity of this catalyst is above the normal range. Needless to say, the consistently low readings challenge the meaningfulness of testing the effectiveness of nicotinic acid in a homogeneous subpopulation selected on the basis of this criterion.

Mauve Factor

Most recently the "mauve factor" was re-identified as 2,4-dimethyl-3-ethylpyrrole by Sohler, Beck and Noval²² by using paper and thin-layer chromatography. Nevertheless, the relationship between the presence of "mauve factor" and schizophrenic Psychopathology could not be substantiated.

In Craig's unpublished study the "mauve factor" appeared across all diagnostic categories, the frequencies being: 11 paranoid schizophrenics—

three mauve; 20 other schizophrenics—nine mauve; four psychotic depressions—two mauve; one manic depressive—one mauve; 14 neurotic depressions—two mauve; 19 anxiety states—nine mauve; and 13 psychoneurotics—four mauve.

The frequency of mauve to non-mauve in the schizophrenics was 12:19, and in the neurotics 13:19. Furthermore, the CNS response to the mauve factor compound, i.e. 2,4-dimethyl-3-ethylpyrrole, was essentially a progressive increase in the baseline EEG-sedation in proportion to increasing the dose (in the rabbit).

In view of this sedative effect—even if the "mauve factor" would be exclusive for schizophrenics—the "mauve factor" was eliminated as one of the possible stimulant metabolites which could produce over-arousal in the schizophrenic patients (Sohler, Beck and Noval²²).

Needless to say that the sedative effect of the "mauve factor" substance challenges the meaningfulness of testing the effectiveness of nicotinic acid in a homogeneous subpopulation selected on the basis of the presence of the "mauve factor" in the urine.

Pink Spot

Counterclaims have been advanced that the "pink spot" is not 3,4-dimethoxyphenyl-ethylamine (DMPEA); that DMPEA is not present in urine from either schizophrenic or normal subjects; that DMPEA is not an endogenous substance but rather a dietary artifact; and that DMPEA is not specific for schizophrenia. The contention that urinary DMPEA has an exogenous plant source—common tea—and is independent of schizophrenia (Stabenau²³), however, was not borne out by the presented evidence (Friedhoff²⁴).

On the other hand a possible link between pink spot and abnormal methylation

reactions in the body was supported by an observation made on a patient who was known to excrete pink spot from time to time and who, when given a monoamine oxidase inhibitor, immediately recommenced to excrete pink spot (Bourdillon and Ridges²⁵).

Furthermore, while in previously conducted studies, orally administered DMPEA failed to induce or precipitate psychopathological reactions in normal subjects or in schizophrenic patients in remission, in more recent experiments, when administered intravenously or to subjects pretreated with a monoamine oxidase inhibitor, DMPEA was shown to have psychotomimetic effects (Charalampous²⁶ and Feldstein²⁷).

In spite of all of these positive findings the relationship between both the pink spot and DMPEA and the presence of the pink spot and schizophrenia are seriously questioned and until these questions are answered there would be no point in testing the effectiveness of nicotinic acid in a homogeneous subpopulation selected on the basis of the presence of the questionable "pink spot" in the urine.

Bufotenin-like Substances

In their latest paper Tanimukai and his collaborators²⁸ reported on bufotenin (4 to 10 $\mu\text{g}/24$ hours), both in free and conjugated forms, in the urine of four schizophrenic patients under dietary control when they were receiving tranlycypromine, with or without cysteine loading. In the absence of monoamine oxidase blockade, bufotenin was also excreted in some patients but less than 1 $\mu\text{g}/\text{day}$.

Increase of urinary bufotenin and other N-methylated indoleamines were observed, however, about two weeks before the mental and behavioral symptoms of the schizophrenic patients worsened and these elevated levels continued during the period of behavioral exacerbation.

In normal controls, under the same conditions,

there was also an increase of urinary tryptamine but chromatograms were negative for bufotenin. This suggested, that in contrast to schizophrenics, normals might not be able to dimethylate tryptamines (Heller et al.²⁹).

In subsequent studies differences were found also between acute and chronic schizophrenic patients. The acutely disturbed patients revealed bufotenin, N,N-di-methyltryptamine and 5-methoxy-N,N-di-methyltryptamine in their blood and urine, but chronic patients failed to do so. Nor did the chronic patients show marked behavioral aggravation in the absence of chemically provoked stress (Himwich³⁰).

Thus *it* seems that normals differ qualitatively from schizophrenics in their inability to dimethylate tryptamine; that acute schizophrenics quantitatively differ from chronic schizophrenics in the rate of formation and/or detoxification of dimethyl-tryptamine analogues.

Independent of their heuristic implications, the exclusive findings of dimethylated tryptamine metabolites in the urine of schizophrenic patients provided for a method which can be employed in the selection of a schizophrenic subpopulation—homogeneous at least on one biochemical criterion—in which the therapeutic efficacy of nicotinic acid might be tested more meaningfully.

Transmethylation Disturbance

With these new positive data on dimethylated phenylalanine and tryptophan metabolites—and independent from the negative data—the idea that transmethylation is the process which may be responsible for the formation of psychotoxic substances (Kety³¹ and Smythies³²), received some further support.

The emphasis during the past nine months, however, remained shifted from

the psychotoxic compound—"mauve factor," "pink spot" and "bufotenin-like" substances—produced by or as a result of transmethylation to the biochemical process itself.

Considering that transmethylation is an all-encompassing process, it is conceivable to suggest that its disturbance may produce such diverse but fundamental and all-embracing changes as are encountered in schizophrenic patients.

The first attempt to identify patients on the basis of abnormality of methylation was made by Buscaino, Spadetta and Carella.³³ By incubating deproteinized blood with betaine as a methyl-donor and nicotinamide as a methyl-acceptor, they found a much greater increase in N-methylnicotinamide formation in the blood of "active" schizophrenic patients than in the blood of normal subjects or of patients with other psychopathological conditions.

In contrast to this by employing radioactive isotope techniques in the identification of patients with an abnormality of methylation, Israelstam, et al.,³⁴ found that the conversion of methionine into carbon dioxide is delayed in schizophrenics.

In a group of normal subjects the peak of $C^{14}O_2$ excretion was after 18 to 25 minutes of the C^{14} -labelled methionine administration, while in a schizophrenic group there was a rising curve for a period of two and a half hours.

Whether any of these subgroups, selected on the basis of excessive or delayed methylation processes, will be therapeutically responsive to nicotinic acid administration remains to be seen. Nevertheless, the testing of transmethylation processes provides for methods which can be employed in the selection of schizophrenic subpopulations—homogenous on the basis of one or another biochemical criterion—in which the therapeutic efficacy of nicotinic acid might be tested more meaningfully.

DISCUSSION

In view of the controversy about the various biochemical methods which could possibly be employed in homogenizing schizophrenic subpopulations—and consequently in the absence of verified biochemical indicators of therapeutic responsiveness to nicotinic acid treatment—the practical decision whether nicotinic acid should be prescribed must still be influenced by careful consideration of the known adverse effects that this treatment may produce.

"Non nocere" is one of the most important principles of the Hippocratic Oath, a principle which is especially relevant in today's competitive therapeutic orientation. The regulative norm must limit the chosen therapy to a favorable ratio between the possible adverse effects of treatment and the definite adverse effects of the untreated disease.

In this context, one must not overlook the fact that schizophrenia is a severe debilitating disease which disables a considerable percentage of the general population. To withhold or categorically deny any treatment which holds some promise—either on the basis of empirical findings, medical thinking or statistical probabilities—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.

On the other hand, the prescription of a therapeutic regime which has shown to be not the optimal treatment for the average schizophrenic patient before the optimal treatment had been tried, may at this stage of development be contrary to the physician's duty. Because of this, it is the responsibility of the psychiatric researcher to establish whether a nicotinic acid responsive group can be identified by the application of available methods.

CONCLUSIONS

The current status of chemotherapy of schizophrenia, with particular reference to neuroleptic and niacin treatment, has been appraised. It was pointed out that, in spite of all its limitations, the treatment of choice for schizophrenia today is pharmacotherapy with neuroleptics.

The recognition, that neuroleptics have helped but not cured the schizophrenic patient, has led to an increasing interest in the testing of hypotheses based on biochemical theories. There are at least five biochemical hypotheses on the basis of

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which the administration of nicotinic acid may have

a therapeutic effect in schizophrenic patients.

Since it was shown that nicotinic acid is not the optimal treatment for the average schizophrenic patient and in the absence of verified clinical or biochemical indicators for therapeutic responsiveness, it was concluded that nicotinic acid should not be prescribed before neuroleptic treatment has been tried.

Whether a group of schizophrenic patients responsive to nicotinic acid can be identified through the application of presently available methods remains to be seen.

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