Myths, Theories and Treatment of Schizophrenia

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INTRODUCTION

It is a remarkable fact, that Bleuler's (1911)[14] concept of schizophrenia has retained its diagnostic and heuristic vitality for more than 65 years. In spite of all the changes which have been encountered during this period, schizophrenia has remained one of the most important psychiatric disorders and one of the greatest public health problems in all developed countries of the world.

Although the lifetime incidence of schizophrenia is close to one percent in the general population, it has been estimated that between one-third and one-half of all psychiatric beds in the United States are occupied by schizophrenic patients (Woodruff, Goodwin and Guze, 1976)[49] with a cost of close to 20 billion dollars a year (Gunderson and Mosher, 1975).[27] The enormous human distress associated with this mental disorder can, of course, not be quantified.

For the therapeutic management of the majority of schizophrenic patients, pharmacotherapy offers higher reliability, easier accessibility, greater simplicity, and fewer hazards than any other treatments known today. Pharmacotherapy of schizophrenia is certainly the treatment of choice for acute and chronic schizophrenics in the community where the uncontrolled pathological behavior of these patients may be unacceptable. For hosptialized schizophrenics, pharmacotherapy is usually the most effective means of cutting the patient's stay in the hospital short, and of preventing future readmissions (Lehmann, 1975).[36]

By now the superiority of pharmacotherapy over other physical treatments, e.g. insulin-induced hypoglycemia and electroconvulsive therapy (ECT) has been shown convincingly (Heinrich, Kretschmar and Kretschmar, 1972),[28] although ECT may still be justified if a schizophrenic patient has failed to improve after 3 months or more on pharmacotherapy. Similarly, the superiority of pharmacotherapy over individual psychotherapy, group psychotherapy, and milieu therapy has been established (May, 1968).[40] Nevertheless, a combination of these therapies with pharmacological treatment may be more effective than pharmacotherapy alone, especially during the rehabilitation and maintenance phases of treatment (Hogarty et al, 1973).[32] The same applies to behavior therapy which has been found useful primarily in the treatment of chronic, institutionalized schizophrenics (Liberman, 1971).[38]

The pharmacological agents that are most specifi-

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cally effective in schizophrenia are the neuroleptic drugs, also referred to as antipsychotics, or major tranquilizers. By their central adrenergic blocking effects, neuroleptics prevent the access of norepinephrine (NE) and dopamine (DA) to their respective receptors, and thereby decrease neural transmission; and by their screening effects on ascending reticular formation and limbic lobe structures, neuroleptics decrease spontaneous motor activity, reduce reactivity to stimuli, and produce blunting of the emotional response (Hollister, 1970).[33] As a result, neuroleptics have considerably transformed the prevailing manifestations of schizophrenia and provided a basis for greater social acceptability of schizophrenic patients.

DISSOLUTION OF A MYTH

Neuroleptics, together with the improvement of milieu in psychiatric hospitals, have considerably transformed the prevailing manifestations of schizophrenia, while the changes in social attitude, together with neuroleptic treatment, have produced an absolute and relative increase in schizophrenic patient population in the community (Ban, 1972).[4] These changes have been re-interpreted by Szasz (1961),[45] who argued, that psychiatry which deals with "problems of living" is inappropriately subsumed under medicine and that behavior we call sick, e.g. schizophrenic behavior, is not physiologically determined.

While Szasz (1961)[45] has considered mental illness a myth, Laing (1967)[35] suggested that schizophrenia is a label, which some people pin on other people to maintain the status quo by "treating as medical patients certain individuals who, assumedly because of the strength of their inner perceptions and experiences, are exceptionally eloquent social critics". Furthermore, in his essay on "Politics of Experience", Laing (1967)[35] has asserted that schizophrenia is not an illness, but a "voyage of inner exploration" on which "often through quite ordinary people", referred to as schizophrenics, "the light begins to break through the cracks in our all-too-closed minds".

The view that schizophrenia is not so much a breakdown as a breakthrough is shared by Dabrowski (1967).[20] He called it "positive disintegration" and considered it as a natural reaction to stress, which replaces usual problem-solving techniques in severe life crises.

Whether schizophrenia is a myth, label, voyage or breakthrough, the fact remains that schizophrenics stood out and stand out in any community they live in. Foucault (1965)[24] described the situation which arose when, in eighteenth-century France, criminals, "schizophrenics" and the indigent were all locked up together — the schizophrenics quickly became highly

visible because they could not conform to the daily prison life.

In contrast to the prepsychopharmacological era, the typical schizophrenic today spends most of his lifetime outside the hospital in the community. Schizophrenic individuals are rather "expensive" for the community they live in. In Walker and McCourt's (1965)[46] study, for example, less than half of the patients (47 percent) were employed at any time after their discharge from the hospital; and even if they obtained employment, only a small percentage, i.e. one-fifth of the entire population, worked at a regular full-time job throughout the six month follow-up period. More important, however, is that while they live in the community,. without appropriate social preparation, they may contaminate the genetic pool by their increase in fertile marriages (Erlenmeyer-Kimling et al, 1969).[23] In this context, however, it is important to note that there is an interference by neuroleptics with sexual functioning.

EVOLUTION OF A THEORY

Considering the stubbornly stable prevalence rate (0.3 percent) of schizophrenia over time and across space, and the fact that the incidence of schizophrenia is much higher among the relatives of schizophrenic patients (7 to 16 percent if one, and 40 to 68 percent, if both patients are schizophrenic) than in the general population, it has been suggested that genetic factors play an important role in the pathogenesis of the disease (Ban, 1973).[5]

In a biochemical genetic study, Pollin (1971)[42] was able to demonstrate that urinary excretion levels of most catecholamines were higher in both members of monozygotic twins discordant for schizophrenia than in normal subjects, while 17-OH steroid levels were higher only in the schizophrenic members of the pairs. On the basis of the findings, the possibility, that the catecholamine elevations were related to the schizophrenic "genotype", and the 17-OH steroid elevations were related to the schizophrenic "phenotype" (the clinical expression of the illness), was raised. Supplementing Pollin's (1971)[42] results, are the findings of reduced monoamine oxidase activity (MAO) in blood platelets of both acute and chronic schizophrenics; and the significantly lower MAO activity of blood platelets in monozygotic twins discordant for schizophrenia, in both the schizophrenic and the non-schizophrenic members of the twins. Hence, Wyatt, Belmaker and Murphy (1975)[50] suggest that the low platelet MAO activity of schizophrenics "is not secondary to being ill, but is genetically related to the liability to be schizophrenic". Of course, low MAO activity could be responsible for the functional excess of dopamine; which is in keeping with the finding, that dopamine receptor blocking agents produce improvement and remission, while MAO inhibiting drugs produce aggravation or exacerbation in schizophrenics.

The dopamine (DA) hypothesis of schizophrenia has evolved from Carlsson and Lindquist's (1963)[15]

original studies, on the basis of which it has been assumed that antipsychotic phenothiazine, thioxanthene, and butyrophenone drugs produce a postsynaptic DA receptor blockade, which yields to a compensatory increase in DA synthesis. Although the theory that catecholamine receptor blockade is the crucial step in the action mechanism of antipsychotic drugs dates back to the early 1960's, it was only recently demonstrated that during the administration of antipsychotic drugs, DA receptor blockade actually takes place (Creese, Burt and Snyder, 1976).[19]

It has been demonstrated, that changes in DA metabolism in the brain are reliably reflected in the concentration of the DA metabolite, homovanillic acid (HVA) in the cerebrospinal fluid (CFS). Since probenecid inhibits the transport system responsible for the removal of HVA from the CSF, the rate of HVA accumulation following probenecid administration is proportional to the turnover rate of DA in the brain. Both baseline level HVA concentration and probenecid-induced HVA accumulation in the CSF have been employed in general and clinical psychopathological studies. While baseline HVA concentration, or probenecid-induced HVA accumulation, is less consistently different from normal subjects in schizophrenic than in manic or depressive patients, carefully conducted studies revealed that neuroleptics have produced an increase in the DA turnover rate with an increase in the probenecid-induced accumulation of HVA in the CSF within the first three weeks. Subsequently, however, no increase in probenecid-induced accumulation of HVA, was seen (Goodwin and Post, 1975).[26]

In keeping with the DA hypothesis of schizophrenia are also the clinical psychopharmacological findings that drugs which increase free DA concentration in the brain produce an increase in perceptual and cognitive psychopathological changes commonly seen in schizophrenics. Perceptual and cognitive psychopathological changes have been induced by l-dopa, the precursor of DA; methylphenidate, a releaser of DA; and amphetamines which produce presynaptic DA release, block DA reuptake, and sensitize postsynaptic DA receptors. In favor also are the findings that α-methyltyrosine (α-MT), the inhibitor of tyrosine hydroxylase activity, which prevents the formation of DA by interfering with the conversion of tyrosine to dopa, and antipsychotic phenothiazines, thioxanthenes and butyrophenones, which inhibit presynaptic DA release, and produce postsynaptic DA receptor blockade, have therapeutic effects in schizophrenics (Snyder, 1976).[44]

IMPLEMENTATION OF TREATMENT

Therapy with Neuroleptics

The accepted treatment of schizophrenia is pharmacotherapy with neuroleptic drugs. There are at least 19 neuroleptics (14 phenothiazines, 2 thioxanthenes, 1 dibenzoxazepine, 1 butyrophenone, and 1 dihydroin-

dolone) available for this purpose in the United States and Canada. In equivalent doses, practically all neuroleptics produce the same therapeutic effect, and whenever slight differences in their overall therapeutic activity might exist, they are only of statistical and not of clinical significance (Lehmann, 1976).[37] But, of course, there are always individual patients who respond better to one drug than to another. On the other hand, although there is not any real evidence that a "depressing" drug like chlorpromazine produces better results in excited patients, or that withdrawn of stuporous patients will respond better to a "stimulating" drug like trifluoperazine, there are indications that thioridazine has slight antidepressant effects and thiothixene has activating properties when given to chronic schizophrenics (Ban, 1977).[9]

Probably, the most important differences among the various neuroleptics are in their differential adverse reaction profiles. Thus, aliphatic phenothiazines such as chlorpromazine, produce more drowsiness and autonomic side effects than piperazine phenothiazines, such as perphenazine, while piperazine phenothiazines produce more extrapyramidal side effects, and they are more potent on a mg per mg basis than aliphatic phenothiazines. Piperidine derivatives, such as thioridazine, resemble the aliphatic subgroup in that they induce more drowsiness and autonomic side effects than the piperazines, however, they tend to produce even fewer extrapyramidal signs, but more electrocardiographic changes, than the aliphatic derivatives. The buytrophenone haloperidol is similar in its action to the piperazine derivatives. It causes few autonomic, but often intense extrapyramidal side effects. The dibenzoxazepine loxapine, and the dihydroindolone molindone resemble also the piperazine derivatives in their action. Finally, of the thioxanthenes, chlorprothixene resembles chlorpromazine chemically and in its effects, and thiothixene is similar in its chemical structure and its action to the piperazine derivatives. Replacement of the phenothiazine by the thioxanthene nucleus, however, decreased the intensity of extrapyramidal signs, and possibly also the mood depressant effects of these drugs.

Acute Excitement

For the symptomatic control of acute excitement, the first dose should be 50-100 mg of chlorpromazine, or its equivalent, intramuscularly, or 100-150 mg orally. Since an acute, uncontrolled excitement must be considered a psychiatric emergency, it also must be treated like any other medical emergency, i.e. the physician should remain in almost continuous contact with the patient, or the personnel entrusted with his treatment, until the emergency has passed (Lehmann, 1976).[37] A parenterally administered neuroleptic drug might be expected to take effect in about 20-30 minutes, an orally administered drug within about 45 minutes. If after this time, the patient's symptoms have not improved, either half of the initial dose or the full dose may be repeated. A further observation or report on the patient's condition, after the same time interval, must then be obtained to determine whether the patient's symptoms are now adequately controlled or whether another dose of the neuroleptic is required. It is important that the pharmacological effect of the first and every other dose, even if it has not resulted in notable symptomatic improvement, not be allowed to dissipate completely before the follow-up dose is administered, so that a gradual accumulation of drug effect will be achieved by means of this staggered medication. Reduction of excitement occurs before any toxic manifestations of the CNS manifest themselves, and so the patient's behavioral status is a good gauge of his individual dose requirements in this acute condition. There may be undesirable autonomic effects, particularly orthostatic hypotension, after the first dose, if the patient is hypersensitive to the drug; but all that is necessary to control this complication in most cases, is to have the patient lie down.

Acute Phase

For the systematic treatment of acute schizophrenic conditions a daily dose range of 400 to 1000 mg per day of chlorpromazine, or its equivalent, is indicated. Smaller doses may sometimes be effective, but the majority of acute schizophrenics will require daily amounts of 400 mg or more orally, given initially in divided and later on in single doses.

There exists a clinical relation between the time of response of certain symptoms to treatment and the dose of the neuroleptic drug a patient is receiving; and this relation can be used as a guide to a patient's individual drug requirement. It has been observed that symptoms belonging into the category of *arousal,* e.g. psychomotor excitement, restlessness, irritability, aggressiveness and insomnia, tend to be the first ones to be controlled by effective doses of neuroleptic drugs, usually within two to three weeks of pharmacotherapy. *Affective symptoms,* for instance anxiety, depression and social withdrawal, respond next, as a rule after five weeks of treatment. Finally, symptoms related to *perceptual and cognitive* functions, such as hallucinations, delusions and thinking disorder, tend to disappear last — in many cases, only after six to eight weeks of treatment.

Two of the most common errors committed in the neuroleptic treatment of schizophrenia are: the use of inadequate (too low) doses and too rapid changes of medication. If an impatient physician changes the drug he is prescribing every two weeks, because he is not satisfied with its therapeutic results, he might never learn what the proper dose and time are for any of the drugs he is constantly changing. A good rule of thumb is *not to change to another drug or treatment,* e.g. electroconvulsive therapy, until the drug that was originally chosen, has been given — at gradually increasing doses — for a period of six to eight weeks, without any noticeable improvement.

Chronic Phase

Once a schizophrenic patient's acute symptoms have subsided, the dose of his neuroleptic should be gradually reduced to prepare him for maintenance treatment, possibly with parenteral or oral long acting drug preparations. After the patient is symptom free, one should aim at maintaining him in remission with single daily doses of 100 to 200 mg of chlorpromazine, or its equivalent. Some patients may be successfully protected against recurrences of their illness with as little as 50 mg of chlorpromazine, two or three times a week, while other patients may require daily doses of more than 500 mg of chlorpromazine to remain in remission (Lehmann, 1975).[36]

Many studies have indicated that the risk of recurrence of schizophrenic attacks is at least twice as great for those patients who stop their medication, than it is for those who continue on maintenance neuroleptic treatment. In keeping with this are the results of a one-year study, carried out by Hogarty et al (1973),[32] in 374 schizophrenic patients stabilized in various maintenance doses of phenothiazines, who found a considerably higher relapse rate in patients given placebo only (73 percent), than in patients treated with maintenance phenothiazines alone (33 percent). Since maintenance therapy in schizophrenia may have to continue over extended periods of time (Davis, 1975),[21] it is not surprising that drug interactions between neuroleptics and alcohol, as well as neuroleptics and other pharmacological treatments have become of practical clinical significance (Ban and Amin, 1976).[10]

Alcohol and Alcoholism

Because of the disagreement about the definition of alcoholism, there are no reliable statistics on the prevalence rate of this condition. A nation-wide survey revealed that 68 percent of adults in America drink alcohol on occasion, and that 12 percent are heavy drinkers. Estimates of the extent of alcoholism, range from five to nine million Americans (Woodruff, Goodwin and Guze, 1974).[49] In view of the rather high prevalence rate of both alcoholism and schizophrenia in the general population, the clinical observation that alcohol may precipitate or aggravate schizophrenia, and schizophrenia may lower alcohol tolerance, are of great practical significance (Ban, 1976).[8] It is only recently, however, that these observations may be explained on the basis of systematic animal and human pharmacological research.

In view of the findings, that the increase in motor activity and euphoria after the administration of low doses of ethanol are probably the results of increased tyrosine hydroxylase activity with increased catecholamine synthesis, and the assumption that in certain individuals the increased synthesis of catecholamines yields to a behavioral disorder in which excessive drinking leads to tolerance, physical dependence, and bodily injury, a catecholamine hypothesis of alcoholism was proposed (Carlsson and Lindquist, 1973).[16] The notion that ethanol in moderate dosages enhances tyrosine hydroxylase activity was further substantiated in animal and human pharmacological studies in which pre-treatment with α-MT, a specific tyrosine hydroxylase inhibitor, prevented the ethanol-induced increase in motor activity. The finding that the locomotor stimulant action of ethanol could be blocked by α-MT in animals, indicates that it is the newly synthesized catecholamines which play the dominant role in the ethanol-induced locomotor stimulation in rodents (Engel, 1973).[22] The catecholamine hypothesis of alcoholism gained substantial support by the results of Ahlenius et al (1973),[1] who found that α-MT antagonizes the ethanol-induced euphoria in man. In a double-blind, placebo controlled, cross-over study, they administered 2000 to 4000 mg of α-MT prior to the consumption of 200 ml of ethanol to 10 normal male subjects. As a result, a significant decrease of alertness, talkativeness, elation and happiness, with an increase of fatigue, was revealed. Finally, taking into consideration that self-stimulation behavior (SSB) is selectively increased by drugs that increase central catecholamines, it has been suggested that alcoholism, and not only the acute effects of alcohol, might be the result of increased catecholamine synthesis that has produced facilitation of SSB.

While the catecholamine hypothesis of alcoholism is based on the assumption, that the increase in motor activity in animals, and euphoria in man, after the administration of low doses of ethanol, is the result of the increased catecholamine synthesis, the catecholamine hypothesis of schizophrenia is based on the assumption that schizophrenic psychopathology is the result of the relative increase of catecholamines in the corpus striatum and limbic lobe structures. Now, taking into consideration that ethanol increases catecholamine synthesis, this could explain the clinical observation, that alcohol consumption frequently precipitates the schizophrenic process, and may also aggravate the schizophrenic episode. Since disulfiram interferes with the conversion of DA to NE and consequently, may increase free DA concentration in the brain, this could explain that aversion therapy of alcoholism with disulfiram sometimes produces schizophreniform psychosis in non-schizophrenics, and relapse in schizophrenic patients in remission (Angst, 1956).[2] On the other hand, since α-MT interferes with the conversion of tyrosine to dopa, and consequently, decreases free catecholamines, this could explain that treatment with α-MT may interfere with the alcohol-induced euphoria and self-stimulation (which could result in alcoholism) while it alleviates the schizophrenic episode.

The average person will require an intake of about 41000 mg of absolute ethanol to achieve a mildly intoxicating level of 1 mg per ml throughout 41000 ml of body water. This so-called "priming" amount is often ingested quite rapidly in order to obtain the desired effect.

Since the maximum ethanol which can be metabolized is 10 ml per hour, at least five hours would be required to eliminate the 55 ml (41000) of absolute ethanol taken at first. It follows that continuation of the same dosage rate, or any dosing rate above 10 ml per hour, would very soon lead to progressively higher and more toxic blood levels. It was assumed that the reason for the linear rate of oxidation of ethanol is the saturation of the liver alcohol dehydrogenase at usual ethanol concentrations. But, eventually this is not the case, as it has been shown that the enzyme is only half saturated during blood intoxication with ethanol, and by no means fully saturated even at near lethal ethanol levels. The zero order kinetics of ethanol oxidation apparently arise from a relatively insufficient supply of nicotinamide adenine dinucleotide (NAD), the rate limiting factor in the chain of oxidation of alcohol to acetaldehyde with a role in the oxidation of acetaldehyde to acetic acid. In favor of this are the findings which suggest, that the rate of ethanol metabolism can be accelerated by drugs which increase the ratio of NAD to nicotinamide adenine dinucleotide phosphate (NADP), or stimulate NAD synthesis, such as alanin and nicotinamide respectively (Ban, 1971).[3] Taking into consideration that alcohol increases catecholamine synthesis in a dose-dependent manner, and metronidazole increases alcohol concentration in the brain by inhibiting alcohol dehydrogenase activity (Manthel, To and Feo, 1963),[39] and consequently, interfering with the conversion of alcohol to acetaldehyde, this could explain the clinical observation, that therapy of alcoholism with metronidazole produces a disproportionate reaction to alcohol in non-schizophrenics, and relapse in schizophrenics in remission. On the other hand, since NAD increases the conversion of alcohol to acetaldehyde and, consequently, decreases alcohol concentration in the brain, the possibility that NAD administration alleviates the symptoms of excessive alcohol consumption and prevents alcohol-induced aggravation of schizophrenia has been raised.

Treatment of Intercurrent Diseases

Cardiovascular disorders, and malignancies are the most common of all diseases, and the interaction between the drugs used in their therapy and neuroleptics has become of major practical importance in the treatment of middle aged and older schizophrenic patients (Ban and Amin, 1976).[10]

Body weight increase, hypercholesterolemia and electrocardiographic abnormalities have been described in the course of maintenance treatment with neuroleptics (Clark, Dubowski and Colmore, 1970;[17] Crane, 1970).[18] All these changes may augment the risk factor in cardiovascular disease, e.g. hypertension and coronary occlusion. Most important in this context, however, are the findings that phenothiazines interfere with the antihypertensive effect of guanethidine; and haloperidol interferes with the action of common anticoagulants.

Finally, since DA is the natural inhibitor of prolactin secretion, the neuroleptic-produced DA receptor blockade leads to an increased concentration of prolactin. Taking into consideration that increased prolactin concentrations may play a role in the pathogenesis of cancer of the breast or thyroid, as well as of malignant melanoma, there is a possibility that maintenance therapy with neuroleptics may interfere with the effectiveness of some of the new anticancer drugs (Williams, 1976).[47]

Other Therapeutic Approaches

The recognition that neuroleptics are not curing schizophrenic patients, that they are not causal treatments, has led to an increased interest in the testing of the effectiveness of pharmacological treatments based on various biochemical speculations and theories of schizophrenia. One of the first of these biochemical speculations with possible therapeutic implications was that of Osmond and Smythies (1952),[41] who put forward the view that schizophrenia is the outcome of stress-induced anxiety and a failure to metabolize the increased amount of catecholamines which results in highly toxic, mescaline-like compounds. Accordingly, it was suggested that 3,4-dimethoxyphenylethylamine (DMPEA), an O-methylation product of dopamine may be responsible for the psychopathological changes in schizophrenics. This speculation was almost forgotten by the time Friedhoff and Van Winkle (1962)[25] found a "pink spot" in the urine of acute schizophrenic patients and identified the pink spot as DMPEA, i.e. the para-O-methylation product of dopamine. While the controversy regarding the nature of the "pink spot" and/or the role of DMPEA in schizophrenia are far from being resolved, the fact remains that treatment with GPA 1714, a gallic acid ester and specific catechol-O-methyl transferase inhibitor, has no effect, or may even have a negative therapeutic effect in schizophrenics (Simpson and Varga, 1973).[43]

An alternative speculation was put forward by Hoffer, Osmond and Smythies (1954).[31] They suggested that adrenochrome, an oxidation product of epinephrine may be the toxic agent responsible for the psychopathological changes seen in schizophrenics. While the controversy regarding the role of adrenochrome in schizophrenia has continued, Hoffer (1970)[30] maintains the importance of the administration of high dosages of nicotinic acid, an N-methyl acceptor substance, to schizophrenic patients for the prevention of excessive epinephrine production, i.e. for restricting the supply of the substance from which the alleged psychotoxic adrenochrome is formed. However, while administration of methionine, a methyl donor given simultaneously with a monoamine-oxidase inhibitor, exacerbates the symptoms of schizophrenia (Ban and Lehmann, 1970),[11] treatment with high dosages of nicotinic acid (3000 mg/day) has no therapeutic effect, or may even have a negative therapeutic effect in schizophrenics (Ban, 1975;[7] Wittenborn, Weber and Brown, 1973).[48]

The idea that transmethylation is the process which may be responsible for the formation of psychotoxic substances regained importance in Kety's (1967)[34] reformulation of the transmethylation hypothesis of schizophrenia. He shifted the emphasis from the psychotoxic compound produced by, or as a result of, transmethylation to the biochemical process itself. Accordingly, he suggested that the disorder of the methylation process is primarily responsible for the psychopathological changes seen in schizophrenics. Of course, the same disorder may lead to the production of abnormally methylated compoundsn e.g. DMPEA and/or bufotenin, which would aggravate the situation by adding their own psychotoxic effects to the already disordered neuronal functions by the abnormal transmethylating mechanism. The transmethylation theory has gained considerable impetus by the findings of an increased urinary excretion of bufotenin and other N-methylated indoleamines immediately before and during aggravation of psychopathological symptoms in schizophrenics (Heller et al, 1970).[29] Nevertheless, the fact remains that while combined administration of betaine, a methyl donor, with a monoamine oxidase inhibitor, exacerbates the symptoms of schizophrenia (Berlet et al, 1965),[13] treatment with a diet containing reduced amounts of tryptophan and methionine has no therapeutic effect in schizophrenics (Berlet et al, 1966).[12]

There are numerous other speculations (e.g. NAD deficiency), hypotheses (e.g. catecholamine, indoleamine), and theories (e.g. plasma protein factor, 6-hydroxydopamine) of schizophrenia with possible therapeutic implications. All specific treatment attempts, based on these speculations, hypotheses and theories, however, have invariably failed, (Ban, 1974).[6]

CONCLUSION

Introduction of neuroleptics has considerably transformed the prevailing manifestations of schizophrenia to the extent that it created a situation in which it was possible to argue that schizophrenia is a "myth". Nevertheless, pharmacotherapy with neuroleptics has corrected some of the biochemical changes, and has altered the course of schizophrenia, but has not cured the disease. In view of this, numerous speculations and theories of schizophrenia with possible therapeutic implications have been proposed. All specific treatment attempts based on these speculations and theories, however, have invariably failed until now.

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