

Allergy, Depression and Tricyclic Antidepressants

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INTRODUCTION

Psychiatrists have been very reluctant to accept the idea that depressions, which they know so well, may be caused by allergies to common environmental molecules such as foods, airborne particles, and chemicals in water. When patients were depressed and anxious, and at the same time suffered from diseases accepted as allergic, psychosomatic explanations were used. This usually meant that a psychological explanation for the presence of the allergic reactions was invoked. The mood disorder was looked upon as a natural reaction to the discomfort of the allergic reaction. Asthma for a long time was one of the seven major psychosomatic diseases. Most psychiatrists still believe schizophrenic patients can not be allergic, at least not when they are ill, but it was accepted that schizophrenia and allergic reactions could alternate.

A few physicians have concluded that allergic reactions are much more common than one would assume from the psychiatric literature, and that the allergic reaction

causes a variety of symptoms of which mood disorder is one. The patient with asthma is not depressed because it is hard to breathe—the depression and the difficulty in breathing are both expressions of an allergic reaction to one or more foreign types of molecules.

Many years ago allergists recognized that it was possible to be allergic to foods as well as to pollens or dusts, and described the mood symptoms which were also present. The depression and anxiety was recognized as a reaction to the allergen, but prime emphasis was given to the non-psychiatric symptoms. Clinical allergists who are now practicing clinical ecology went one step further when they recognized that allergic reactions could cause depression and anxiety as the main symptom with minimal somatic reactions.

Dr. T. Randolph (1961, 1966) observed a large number of allergic depressions. Manic-depressive psychosis, in his opinion, is a cyclical reaction to a number of allergens ranging from foods to airborne pollutants. But psychiatrists are unaware of the contributions made by clinical ecologists such as Randolph (1965), Mandell and Scanlon (1979), and reject the observations of clinical

psychiatric ecologists such as Newbold (1975) and Philpott (1974, 1979) as well as Sheinkin, Schacter and Hutton (1979).

In this communication I will summarize the evidence which supports the conclusion that a large fraction of depressions are responses to environmental molecules, and that the tricyclics are effective in many patients because of their antihistaminic properties, not because they act upon the serotonin or sympathomimetic amine pathways.

DEPRESSION IS A SYMPTOM OF ALLERGIC REACTIONS

Most patients with somatic symptoms of allergy have a mood disorder, usually depression and anxiety. I can not recall a patient with asthma, with a severe allergic itch, or suffering from hives, who was happy. They all had depression and anxiety ranging from slight to very severe. Psychosomatic explanations have a long and honorable history but are no more firmly established today than they were when they were so popular thirty years ago. They have no predictive value, do not indicate treatment, and no patient is better because of them. The fact that it makes sense that depression should be a response to the somatic symptoms does not make this true.

Clinical ecologists who had little interest in psychiatry described depression as a common problem in allergic reactions. Rowe and Rowe (1972), pioneers in establishing food deprivation tests to locate foods which were being reacted to, wrote that symptoms include "lack of energy and ambition, drowsiness, loginess, depression, inability to think and concentrate. Temper tantrums and emotional instability may be present."

I became interested in the relation of allergies to depression about ten years ago. I also observed that patients who were found to be allergic usually were depressed. A psychiatrist who neglected to take a history of allergic reactions would have diagnosed them as a mood disorder. Later I observed that over half of all the patients who were referred to me because they were depressed, and who were in fact depressed, had a history going back many

years of somatic allergies. As children they had eczema or rashes, frequent upper respiratory problems, and asthma or hayfever. Most were aware of these symptoms which had been treated by their physicians but none associated the history of allergic reactions with their current mood disorder. I checked this with a colleague who was known as a specialist in depression but who did not practice Orthomolecular psychiatry. He too was amazed at the high incidence of somatic allergies in his depressed patients. The association is so high that any psychiatrists will corroborate it in a few months of observation. All that is required is to include allergies in the history of the patient.

Allergic reactions may become addictive reactions. This is the basis for the craving for sugar, alcohol, and even for foods such as milk or meat. The most accurate way of diagnosing a food allergy is to deprive the patient of food for a number of days; usually four but sometimes many more are required. This is done by fasting the patients or placing them upon a diet of foods that they have used very rarely (Mandell, 1979). Deprivation of the food until all traces are gone from the gastrointestinal tract will result in a reduction of all symptoms or in their complete removal. Patients who have food allergies often feel normal toward the latter part of the fast. When I fasted four days about six years ago I expected to feel hungry and irritable the whole four days. For two years I had suffered from a chronic cold and difficulty in breathing. I was unaware I had an allergy and fasted for other reasons; to my surprise I was euphoric the fourth day and my cold was gone. I subsequently discovered I was allergic to milk products.

The first part of the fast is generally unpleasant; there is a withdrawal reaction like that suffered by a heavy smoker when smoking is stopped abruptly, or like 'cold-turkey' heroin withdrawal of which the addict is so fearful. During these few days, patients miss the repeated stimulus of the foods they normally eat to which they are allergic; in a few patients the withdrawal from these foods has been very severe. One of my patients consumed twelve glasses of

milk each day—it kept her going. I was then inexperienced in the technique and results of food deprivation and I advised her to discontinue milk immediately. Within five days she was in a deep psychotic depression and I had to admit her to hospital to protect her from killing herself. Since then I have withdrawn patients slowly, over a period of a month, if they consume large quantities of any foods. The consumption of large quantities of food—bread, pastry, sugar—is a clear indication to suspect these foods as one of the causes of depression and anxiety.

Withdrawal depression will also account for the diurnal rhythm of depression. Most illnesses are made worse by fatigue; schizophrenia and physical illnesses tend to become worse in the evening as patients become more tired. Depression, in sharp contrast, tends to become better at night. It is common for depressed persons to feel awful in the morning; they are tired, anxious and depressed. As the day continues they gradually feel better; after supper they often feel almost normal. What likely happens is this: in the morning the patients are suffering from withdrawal, having had no food for 12 hours or so; during the day foods to which they are allergic are consumed, and by evening there is no further withdrawal reaction. Each day the cycle is repeated.

Treatment of the allergy will, in most cases, "cure" the depression. I have seen this in several hundred patients over the past six years and can no longer doubt this conclusion. About six years ago a chronic psychotic depressive patient was referred; he had been deeply depressed for four years. During that time he had failed to respond to a series of ECT in a psychiatric ward. He was maintained on injectable tranquilizers which partially controlled his anxiety but left him incapable of doing more than eating and sleeping in a sheltered environment. I diagnosed him as a depression with schizophrenic features. He did not respond to Orthomolecular vitamin treatment. After a four day fast he was normal and one month later was back at work as a high school teacher—he had not been able to work for five years. The four day fast and subsequent testing showed he was allergic to

cigarette smoking.

Subjects who are free of depression will note a sudden resurgence when they eat those foods they have been avoiding either by accident or deliberately. I have found that January tends to bring back a large number of my patients who were well but who gave way to the holiday foods so abundant in December, primarily junk foods or food artifacts.

I have referred to a number of associations which support the contention many depressions are symptoms of allergic reactions.

1. Clinical ecologists observed a high incidence of depression in their allergic patients.
2. I observed that a large proportion of depressed patients had earlier in life suffered from a variety of somatic allergies.
3. Removal of offending foods or other molecules resulted in relief from depression.
4. The typical diurnal pattern of deep depression in the morning and relief in the evening can be explained by the overnight withdrawal from foods one is allergic to.
5. Depression is common following exposure to allergic foods and may come on within a few minutes.

THE TRICYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants are third generation antihistamines. The discovery of the antihistamines was followed by their use as tranquilizers. Dr. H. Laborit (Caldwell, 1970) was looking for a centrally active sedative. As a direct result of his interest chlorpromazine was given to the first patient January 19, 1952. It is curious that our first use of large doses of vitamin B3 came only a few months later. But chlorpromazine was patented and owned by a drug company while vitamin B3 was public domain.

However, the idea of using antihistamines preceded chlorpromazine by at least three years. A report appeared where it was claimed that an antihistamine, benadryl I believe, was combined with ascorbic acid and helped a small number of schizophrenics.

A subsequent report failed to corroborate, but the idea was already in the medical literature. Failure to corroborate is very often a function of the intent of the person who failed.

It was known shortly after the early antihistamines became available that they had sedative properties; these were undesirable. The companies wanted a substance with no sedative properties and maximum antihistaminic effect. Dr. H. Laborit, a surgeon, wanted just the opposite. Chlorpromazine represented the first member of this new class of compounds which had much more central sedative effect and less antihistaminic effect. From France the tranquilizers rapidly spread into Canada and later into the U.S.A. Dr. H. Lehmann's report first hit the English literature a few months ahead of an American investigator.

Psychiatrists did not receive tranquilizers gratefully, for they were rapidly swinging to the view schizophrenia was a psychosocial disease with insignificant biochemical features. In this they were led by the National Institute of Mental Health. This analytically led and inspired group only began to fund tranquilizer studies after immense pressure from a large group of senators and congressmen.

This is an early example of the use of political pressure to achieve a psychiatric improvement. Tranquilizers were a distinct step forward.

Antihistamines fathered the tranquilizers and later the tricyclic antidepressants. Imipramine was synthesized in 1948. It is like a phenothiazine tranquilizer with antihistamine properties. Kuhn (1957) reported its antidepressant properties. Sigg (1968) summarized its properties:

- (a) It was like a weak phenothiazine tranquilizer.
- (b) It potentiated the action of noradrenalin interfering with uptake and binding. In this it resembles phenothiazines and antihistamines.
- (c) It augments or prolongs many effects of amphetamines and methamphetamines such as motor activity and hyperthermia. Phenothiazines in

contrast decreased these effects. Imipramine resembled the antihistamines.

- (d) It caused ptosis as did antihistamines.
- (e) It interfered with the histaminergic system.

Sigg discussed previous suggestions that the antidepressant action of imipramine was due to central antihistamine properties while noting that certain antihistamines were antidepressants. In fact I have treated a patient whose addiction to antihistamines was as powerful as any heroin addiction. Sigg finally concluded that the antihistamine effect was not a factor "because clinically demonstrated antidepressant action seems inversely correlated with antihistaminic potency." But then the concept of cerebral allergy was unknown. There is no necessary correlation between central and peripheral antihistamine activity. Since Sigg's review, antihistamine activity of tranquilizers and antidepressants has been more or less ignored.

However, a new potent antidepressant has appeared. Mianserin is described in an issue of the **British journal of Clinical Pharmacology**, edited by Peet and Turner (1978). It is as effective an antidepressant as imipramine or amitriptylene but has fewer side effects. It is not an anticholinesterase. In the following Table I have listed its properties and these are compared with the usually accepted properties of the tricyclic antidepressants.

It is clear we have a new antidepressant which does not share with the tricyclic antidepressants the usual effect on catecholamines and on serotonin metabolism. They only have antihistamine properties.

Imipramine has been used to treat a number of allergic diseases (Angst and Theobald, 1970). Given intramuscularly, 25 milligrams partially protected patients against histamine inhalation. It has been used as an adjunct for treating asthma and has been recommended for the treatment of various aspects of asthma. It decreases the size of histamine induced weals. It is a potent antagonist of histamine and brady-kinin. In fact, all tricyclics have moderate to strong antihistamine activity. Mianserin has also been used for treating

TABLE 1 COMPARISON OF MIANSERIN AND TRICYCLIC ANTIDEPRESSANTS

Property	Tricyclics	Mianserin
a) On Catecholamines		
1. Potentiation		
i. amphetamines	potentiates	antagonist
ii. apomorphine	potentiates	no effect
iii. dopa	potentiates	no effect
2. Brain Noradrenalin Availability		
i. chronic administration	Increased by inhibition of uptake	increased by effect on release
ii. turnover	reduced	increased
b) Serotonin potentiation	yes	inhibition
c) Antihistamine	yes	yes

asthma (Peet and Behagel, 1978). Asthmatics given Mianserin had fewer night attacks. This finding was not pursued because of side effects, i.e. centrally antidepressant effects. Mianserin is an effective antidepressant which does not have the two main characteristic actions of tricyclic antidepressants on catecholamines and serotonin, but is a good antihistamine.

TREATMENT OF FOOD ALLERGY BY TRICYCLIC ANTIDEPRESSANTS

Patients who have one or two food allergies are easily diagnosed and treated; after the foods are identified they are avoided. I have avoided all milk products for six years with little difficulty and have not had a "cold" since then, but many patients have multiple food allergies and a few seem to react to nearly everything. They are very difficult to treat successfully and a variety of procedures have been developed.

Special Diets

Of these the rotation diets have been most successful. However, there is a lot of patient resistance toward these, and their families may also resist. They tend to make patients totally preoccupied with food and eating, and often they simply do not work. Fasting has been used; I have had several patients who were much improved by a four day fast who had no food allergies on subsequent tests. On returning to their no-junk diet

which they had been on before the fast they remained well for a long time. The fast appeared to have a clearing function.

Vitamins

Some of the vitamins have anti-allergy properties and have proven helpful. Niacin releases histamine and lowers histamine levels in the body. I have observed in many patients that they required very large doses of niacin, 1 to 12 grams per day or more, until they eliminated those foods they were allergic to. In many patients, eliminating milk promptly reduced the amount of niacin that was required and could be tolerated from 12 to 3 grams per day. Ascorbic acid reacts with histamine in vitro and presumably in the blood; it rapidly inactivates it. It has been very helpful in dealing with allergic reactions associated with insect bites, rashes, etcetera.

Enzymes

Ideally, foods which are completely digested to their component amino acids, sugars, and fatty acids ought not to cause allergic reactions. If, however, larger fragments are left, dipeptides or disaccharides or other more complicated molecules, then one would expect more allergic reactions. These larger fragments can easily cross into the blood and even into the brain, across the blood/brain barrier; this has been established by tracer studies.

Perhaps these large or macro-molecules are responsible for the toxic reactions to some food. Following this line of reasoning it is possible a deficiency in the secretion of digestive enzymes, either from the pancreas or the intestinal walls, might be a factor; finally it would follow that replacing these enzymes would be helpful. Some of my patients have been helped and I have several who are able to eat foods which previously made them ill; they took pancreatic enzymes before eating. But others were not helped and several suffered allergic reactions to the enzyme, either to the capsule, its color, or to the contents. But patients who have been helped remain very grateful. We require careful, large scale clinical trials to examine the therapeutic role of enzymes and nutrient supplements.

Tricyclic Antidepressants

In a recent paper (1979) I described the use of an antidepressant, Clomipramine, to treat obsessions and depression. There I suggested that antihistamine properties of tricyclic antidepressants played a role and I referred to several patients whose multiple food allergies came under control by using small daily doses of tricyclic antidepressants. I suggest these antidepressants should be tried when other therapeutic measures have failed.

Imipramine has been used for treating children's allergies even though clinicians using it this way have been unaware of the relationship. Imipramine has been effective in treating enuresis in children but not every child responds. Gerrard (1973) established that enuresis in some children is due to an allergic reaction of the bladder. It becomes smaller, presumably due to increased tension and thickening of the bladder wall. When the offending food is removed the bladder relaxes and in a few weeks they are normal. Reintroducing the offending food, often milk, quickly reestablishes the bed-wetting problem. Perhaps these are the children who responded best to imipramine.

I have also used tricyclic antidepressants for obesity and to control voracious appetites

for certain foods, as well as for a number of somatic allergic reactions.

Many obese patients have a voracious appetite for foods to which they are allergic. They will eat a loaf of bread in an hour, will drink 16 glasses of milk in a day, will eat a pound of chocolate in a few minutes. These are allergic reactions gone wild and have become severe addictions. I have found that for many of these the tricyclics help reduce the intensity of the desire for these foods, and have helped many obese patients bring their weight down slowly.

Antidepressants may be very helpful in treating children with learning and behavioral disorders; probably half of these children suffer from cerebral allergies. Speer (1970) described the allergic tension state as "a clinical allergic state which is marked by diffuse neuropsychic overactivity. It includes both a motor component (hyperkinesis) and a sensory component (hyperesthesia). Usually both are present in the oversensitive allergic child."

CONCLUSION

Tricyclic antidepressants are antidepressants largely because of their antihistaminic properties. This conclusion is based upon the following observations:

1. The close association between depression and allergies. It is rare to find one without the other; when one is relieved, so is the other.
2. Mianserin is a powerful antidepressant which differs from the tricyclics in having no effect on the metabolism in the brain of catecholamines or serotonin. It is a good antihistamine, a property common to the tricyclics as well.
3. Tricyclic antidepressants are useful in treating allergic reactions no matter what form they have taken. This ranges from allergic addiction such as obesity to enuresis.

I suggest neuropsychopharmacologists once more examine seriously the antihistaminic properties of the antidepressants.

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