Allergies and Schizophrenia: Immune System Starvation ?

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Summary

A possible genetic link between certain Type I atopic allergies and some forms of thought/behavior disturbance and/or schizophrenia was explored through a 19-month trial of high dosage nicotinic acid in an allergic subject with a familial history of atopic allergies and schizophrenia in different individuals.

The asthma and allergic rhinitis of this subject were controllable by niacin in the presence of known allergens. Niacin dosage needs, after an initial rise, displayed a downward inclination. After a period of violent exacerbation, the eczema healed and did not recur. Allergic rhinitis almost totally disappeared, and asthma was moderately frequent but of minimal severity at the conclusion of the trial. Other suggestions of internal healing processes were indicated.

Results focus on a variation of the biogenic amine hypothesis for schizophrenia, and incorporating atopic allergies, through a combination of genetic abnormality in amino acid metabolism and the environmental stress of nitrogen-depleting infection, leading in a downward spiral to chronic immune system exhaustion.

Tryptophan/niacin metabolism is again implicated (Gilka, 1975), prompting abnormal feedback reactions on the tyrosine metabolic pathway (Fig. I) in individuals who present mental alterations rather than atopic allergy, and schizophrenia is seen as an extreme pole in a continuum of immune system starvation, with the variable factor as an inability to produce autoantibodies to the beta-2-adrenergic receptor proposed by Venter et al. (1980), or a similar deficiency-activated irregularity (Philpott, 1977; Lee et al., 1980); since a negative correlation between allergies and schizophrenia has often been suggested (Baldwin, 1979).

This trial suggests that "allergic" reactions and some thought or behavior disturbances and/or schizophrenia may be corrected by defining the error in amino acid metabolism or identifying the infection-induced deficiency and supplying the proper nitrogen-bearing substance(s) to restore a balance of health.

Basis

The genetic factor in both allergies and schizophrenic conditions suggested by Kall-

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man (1938) and the NIAID Task Force Report (U.S. Dept. of HEW, 1979), unexplained exacerbations and remissions in symptoms of both, the schi zophrenic susceptibility to tuberculosis (Kallman, 1938), and the history of niacin/pyridine use in treatment of all three (Beumer, 1979; Chyrek-Borowska et al., 1978; Hoffer and Osmond, 1966; Molcan, 1978) prompted the present study, based on the theory that pyridine-3-carboxylic acid, functioning as the natural metabolite nicotinic acid, may enhance immune system response.

Pyridine is a nearly-forgotten asthma remedy, listed as such in medical dictionaries prior to the mid-1940s, although the pyridine ring is found in antihistamines and is present in a new aerosol treatment for asthma: Pirbuterol (Beumer, 1979).

Isoniazid and niacin have been used in treatment of tuberculosis. Pyridine, niacin and derivatives have also been used in other widely dissimilar conditions over the years (Wilson, 1956). Niacin has been used in the past 25 years by megavitamin therapists and orthomolecular psychiatrists in treatment of schizophrenia (Pauling, 1979), although this therapy was severely criticized by the American Psychiatric Association (1973).

A basic immune system involvement is suggested on the basis of the following evidence:

Major nitrogen compounds derived from tryptophan and tyrosine amino acids include the hormones thyroxin and epinephrine/ norepinephrine, and the pigment melanin, all from tyrosine; and niacin, a co-factor for enzymes and transport proteins, precursor of NAD+ and NADP+, from tryptophan. (In plants, codeine and morphine are developed from tyrosine, and the alkaloids quinine and strychnine from tryptophan.)

Both tyrosine and tryptophan contribute to the production of Acetyl CoA, and then to production of cholesterol and the adrenal steroids. Tyrosine is also a precursor of epinephrine and norepinephrine. Both the adrenal steroids and epinephrine are potent anti-allergy substances, and additionally, dopamine and norepinephrine are neurotransmitters in the brain. A third important neurotransmitter is serotonin, a product of tryptophan metabolism on an alternate metabolic pathway (Fig. I) (Meltzer, 1979.)

The onset of both Type I allergies and schizophrenia is often preceded by severe environmental stress, frequently in the form of infection.

Many studies link brain function and allergy, deliberately or circumstantially, from Hoffer (1977) to Rudin (1979), Carr et al. (1978), Cattaz and Beckmann (1980), Mathe et al. (1980), Misur and Takao (1978), Fessel et al. (1965) and Newbold et al. (1973), to cite a few.

Tryptophan and niacin are essential for nitrogen equilibrium in adults and for growth in children. It is said that childhood asthma can retard both mental and physical development (U.S. Dept. of HEW, 1976) and it has been reported that the adult schizophrenic whose condition began in childhood is of generally smaller stature (Hoffer and Osmond, 1966).

A deficiency of niacin and tryptophan interferes with antibody formation (Scrimshaw, 1979), and niacin deficiency is likely to impair tissue integrity. Powanda (1977) finds "a purposeful redistribution [of nitrogen] from peripheral to visceral tissues for various aspects of host defense."

Nicotinic acid is a co-enzyme of NAD, and in a recent paper, Bull et al. (1978) suggest that NADases regulate the rate of certain metabolic processes by controlling levels of oxidized nicotinamide coenzymes, and that there is support for additional regulatory roles for these enzymes.

Nitrogen losses during infections are well documented (Scrimshaw, 1979).

Amino acids are the center of nitrogen metabolism, and a genetic irregularity in amino acid metabolism might affect specific nitrogen bonding. Powanda (1977) points out that systemic metabolic alterations induced by the anorectic state in illness and host defense, exaggerated by malnourish-ment, often lead to reduced host defense mechanisms, phagocytosis and cell-mediated immunity. He sees nitrogen as a requirement for host defense.

Lending further credence to a nitrogen depletion hypothesis for schizophrenia is documentation of changes in nitrogen balance

in the rare condition of periodic catatonia, although those studies were not successful in identifying a nitrogen abnormality in ordinary schizophrenia (Lewis, 1963).

Recent research identifies a niacin/tryptophan abnormality in rheumatoid arthritis (Labadarios et al., 1978), and this condition is one of those negatively correlated with schizophrenia (Baldwin, 1979). Systemic lupus erythematosis (Carr, 1978; Schur, 1978), with its allergic connotations and mental involvement, may also be a related condition, perhaps with stronger genetic overtones. Pellagra, a deficiency disease cured by niacin, evidences mental damage.

Subject History

The subject of this trial, a 44-year old female, had a long-term allergic history involving asthma, allergic rhinitis and eczema. She first experienced allergic rhinitis at the age of seven, two years after the removal of tonsils, which in turn had followed a series of infections. Asthma at age nine was immediately preceded by a severe bronchial infection.

There was some remission on moving to another state, except for a six-month exacerbation preceded by a severe bout with pneumonia, and again with a six-month exposure to cats. Contact with animals was at least a contributing factor in all exacerbations through the years, although certain molds and pollens were also major offenders.

Allergy scratch tests in 1958 and 1977 identified 4+ sensitivity to horse hair and dander, 3+ to cat hair and dander, along with 3+ to house dust mixture (intradermal). The more extensive 1977 tests found 3+ and 4+ reactions to several pollens and molds; numerous 2+ reactions, including dog hair and dander; and many other 1 + and trace sensitivities.

The problems returned in the form of allergic rhinitis when the subject moved back to her home state in 1969, and gradually worsened through the next nine years, until niacin treatment was begun on January 20, 1979.

The renewed hay fever responded to non-prescription medication until late 1973, some two years after again acquiring a dog and cat. The subject was adamant in her refusal to again part with the pets, considering animals an important part of the family's life (the subject was, in fact, later the founder of a county humane society).

Eczema began in 1973, for the first time in the subject's experience, along with a reoccurrence of asthma. Both required prescription medication by late 1974. Eczema was primarily on the palms of the hands, with some minor affliction developing later on the face and arches of the feet.

All three conditions were thereafter controlled with standard allergy medications in generally increasing amounts, although a change from marax to aminophyllin for treatment of asthma did seem to eliminate the need for injections of the epinephrine and steroid type drugs.

Desensitization injections were begun December 9, 1977, continuing through April 6, 1979, about ten weeks after niacin treatment was begun. These had seemed to have had little or no therapeutic benefit, however, and desensitization to animal hair and dander was not attempted.

Niacin treatment in 1979 brought about a progressive improvement in the allergic conditions, even in the presence of allergens, documented by drug purchase and use records (Fig. II).

Family History

The subject's father, deceased, is known to have had asthma and eczema. He also had rheumatic fever as a child.

The subject also had a maternal uncle and a cousin (female) with mental conditions presumed schizophrenic. Two paternal uncles are said to have died from tuberculosis. The subject herself is an only child.

The subject has four children, three now adults. None have clinically defined allergies, although mild respiratory congestion has been suspected as allergic in origin for two daughters in recent years. The allergic subject has never been diagnosed as having psychiatric difficulties, nor have the three daughters.

The only son, however, has been variously diagnosed as delinquent and as "borderline"

schizophrenic. A recent test for systemic lupus erythematosis did not yield positive results.

The subject's son has a paternal uncle with narcolepsy and a male cousin in that line with a hyperkinetic condition.

In no case is an individual known to have both allergies and mental disturbance.

The subject notes that her son displayed dilated pupils of the eyes from age two onward, in conditions not associated with available light; ran sudden and alarmingly high fevers when ill until about age four, and was rarely sick thereafter except for scarlet fever at age 10 or 11. He did have about three other episodes of unexplained body-wide fine rash between ages 10 and 13, each lasting a few days and itching intensely, with no firm diagnoses.

As a small child and onward, the son is said not to have reacted to mosquito bites with the normal itching, inflammation and edema—a possible correlation with high somatic levels of corticosteroids. The dilated pupils also suggest high tyrosine/epinephrine activity, screening out ultra-violet—in contrast to the SLE patient, who may be sensitive to ultra-violet.

Behavior problems became acute in teen and early adult years. The first diagnosis of schizophrenia was made at age 24: At age 26 he developed a "butterfly rash" and was tested for systemic lupus erythematosis. An initial ANA test was questionably positive, but two subsequent tests were negative.

An executive profile blood study January 20, 1981, also revealed high triglyceride levels (245 MC/DL), which can be correlated with SLE with neurologic dysfunction, according to Falko et al. (1979).

The subject's son did not formally participate in the nicotinic acid trial. However, nicotinic acid has had claimed success over a period of years in treatment of schizophrenia (Hoffer and Osmond, 1966), which was of interest in this case.

Also, the son did independently experiment with niacin during a six-week period in 1980, consuming a total of 36 grams during that period—an average of less than a gram a day, with a high of two grams in a single day. It was three months later that he exhibited the butterfly rash typical of SLE. It cannot be known whether niacin even at this low dosage may have facilitated immune system production to some imperfect degree, while simultaneously reducing the need for a somatic epinephrine and corticosteroid response, and possibly contributing to the lupus-like manifestation.

Suggested as a metabolic abnormality in the allergic subject is the autoantibody to the beta-2-adrenergic receptor proposed by Venter et al. (1980), causing adrenergic hyperresponsiveness.

Suggested as one of the deficiencies in the son's thought-behavior disorder is the absence of this malformed antibody (autoantibody), permitting adrenergic hyperresponsiveness in the brain, in a system almost perpetually engaged in high-level immune response with accompanying high levels of somatic dopamine and/or epinephrine/norepinephrine, and perhaps corticosteroids or phenylalanine.

Cerebral norepinephrine is discussed by Harik et al. (1979).

Trial

Niacin was chosen for this trial rather than niacinamide because of its probable lower toxicity (Jaus, 1977). The allergic subject was pre-menopausal and there were no indications of menopause before, during or following the trial, therefore no reason to believe that major hormonal changes were affecting the results of the trial or condition of the allergies.

The allergic subject was begun on the niacin program January 20, 1979, a low-allergy season for this subject, but still in the presence of allergens; the subject and family occupied an old house with several areas of dampness and wood rot, sharing the dwelling with two dogs and four cats, and having contact with a pony belonging to one daughter, stabled a few blocks away.

Niacin dosage proceeded on an "as needed" basis, in response to allergic symptoms, after an initial buildup of tolerance. It was possible to discontinue standard allergy medication at the outset, although there were a few days of moderate allergic discomfort. No other medication or vitamins

were used or necessary for the first three months.

Dosage began at 200 mg daily in divided doses, gradually increasing. Symptoms were under good control at 200 to 500 mg daily through the three-month pilot period.

In mid-April, when it was well established that niacin alone was controlling the allergies, a high-potency multi-vitamin and mineral supplement was added to the program on a daily basis to help avoid nutrient imbalance as dosage rose. This supplement was continued through the balance of the trial (Formula VM 75, Solgar Co., Inc., Lyn-brook, N.Y. 11563).

Dosage needs climbed during May, and rose sharply during June and July, onset of the midwest "hay fever" season, reaching levels of 6 to 91/2 grams daily for effective control of symptoms in July, with an average daily dose of 65/6 grams during that period.

When niacin-induced discomforts developed on high dosage, supplemental allergy medication was used, usually at day's end, rather than additional niacin. On a few occasions when discomfort intensified, niacin was briefly discontinued until symptoms subsided. This accounts for higher usage of standard medications than would apparently have been necessary otherwise (Fig. II).

An executive profile blood study July 23, 1979, indicated slightly below-normal thyroid function and minimal but definite excesses of several enzyme levels (especially SCOT, alkaline phosphatase, LDH) and uric acid. These were considered indicative of an enhanced immune response through high nicotinic acid supplement.

During this period of high niacin intake, the subject reported intense hunger. She carried high-protein snacks and observed that many discomforts of the niacin treatment, even the gastro-intestinal effects, were often alleviated by eating.

Discomforts included some light-headedness, occasional gastric distress of varying degrees; and late in the trial, heart palpitations and arrhythmias, the latter two occurring when some time had elapsed since intake of either niacin or allergy medication, and seeming to indicate a new type of allergic response (Rea, unpublished; Rea et al., 1978). A possible magnesium deficiency activated by somatic adrenalin (Turlapaty and Altura, 1980) was considered. Blood samples were analyzed for both magnesium and manganese levels, but results showed high-normal levels of both. However, hair analysis was not done.

The palpitations and arrhythmias seemed temporarily controllable by intake of either niacin or aminophyllin, suggesting an allergy-cardiac connection, although the long-term high niacin use is supposed to have been the precipitating.factor (Stamler, 1977; American Psychiatric Association, 1973, page 43).

Throughout the program, reactions in the eczema-afflicted areas were watched closely. During early niacin administration, rash appeared on the face along with the customary "niacin flush." This changed in form several times, then the skin entered a brief period of fine white scaling, the entire syndrome fading and disappearing within several weeks. These effects were not severe or seriously disfiguring.

Next blisters and small pustules appeared on the palms of the hands where eczema had been severe and of long-term duration. This condition gradually became an overall inflammation in the next five to six months, accompanied by itching so severe that patches of epidermis were regularly peeled off by scratching. The distinctive feature was the fact that breaking open the skin appeared to put an end to the itching, whereas in ordinary eczema, scratching is only destructive.

Despite this discomfort, the subject opted to continue the trial, since there was some evidence that this reaction was progressing in the direction of healing, and that the skin may have been ridding itself of inappropriate or toxic deposits accumulated through the earlier years of affliction.

Topical cortisone was used during periods of severe reaction. This did provide relief and did not seem to retard the healing process, since it was used on only one hand *for* quite a period of time, yet both hands ultimately cleared at the same rate. The arches of the feet cleared later in a similar manner.

After ten months of treatment, skin on hands and feet had healed, was of normal glossy texture, and there was no itching. There has been no further reoccurrence of eczema in the following 19 months, through the balance of and after the trial.

Throughout the trial there were various isolated instances of immune action in the skin, apparently as residues from other minor infections of the past exacerbated and then healed. Some slight pigmentation in the armpit areas and between the toes scaled and peeled.

Niacin need decreased considerably by autumn of 1979, but early in 1980 the subject began experiencing some renewed gastric discomfort even at 3 to 3 1/2 grams daily. Dosage was reduced, but discomfort increased even at 1 to 1 1/2 grams, and dosage was interrupted for several days until symptoms subsided. (A blood study indicated high MCV, SCOT, LDH, GGTP and alkaline phosphatase, with low T-4).

Dosage resumed at low levels, and approximately one gram daily controlled allergic manifestations, but heart palpitations and arrhythmias, mild, developed prior to allergic attacks, gaining in intensity through June, 1980. Niacin use was again discontinued and it was found that no allergy medication was needed for several days. Later, very small amounts were needed through early August. The cardiac effects, meanwhile, subsided.

Niacin use was cautiously reintroduced at the rate of about 100 to 150 mg daily, but again the arrhythmias appeared along with some other subtle discomforts which had been developing during that spring and summer.

These included a sensation of fullness or tightness in the upper chest and throat areas, some muscle weakness and/or stiffness with an occasional slight lack of coordination, and shortness of breath without wheezing. There was also an apparent mental effect; the subject reported brief periods of something which may have been a form of thought-blockage, accompanied by quite acute depression, and the subject stated she did not feel like talking at these times. These feelings seemed quite intense, although of brief duration, and sometimes seemed responsive to aminophyllin.

This very vague information may indicate some effect of niacin on serotonin, dopamine or norepinephrine levels in the brain. An association with extrapyramidal symptoms in the expression of "muscle weakness and/or tension" is also tempting.

Two more brief attempts to renew niacin treatment were unsuccessful for the same reasons of discomfort. Since the present effort was privately funded, means of conducting all proper tests were not available, and it was decided at the end of August, 1980, to terminate the trial after slightly over 19 months.

However, the subject did experimentally resume some niacin use, alternating with standard medication when needed, serving to complete the medication record chart for 1980 and the first half of 1981. The increased ratio of standard medication to niacin in that period, as compared with 1979, is of course due to the reduced use of niacin when arrhythmias occurred. (Fig. II.)

The subject reported no further incidence of the tensions, feelings of fullness, depression or other unexplained problems.

At the conclusion of the formal trial, the subject was in apparent good to excellent health, with fewer allergic symptoms than before: no eczema, rare allergic rhinitis, and asthma of minimal severity, easily responsive to light doses of aminophyllin.

Conclusions

Niacin did control this subject's allergies in direct response to the presence of allergens. In the long term it had an apparent curative effect, but seemed to create some cardiac problems.

Termination of the trial left unanswered the question of whether or not this final nia-cin-induced irregularity was also the result of an internal healing process, which might have resolved itself with continued treatment, or become intolerable or even

dangerous, or was due to some other cause. It is quite probable that other deficiencies and imbalances could accrue in this proposed syndrome, or during treatment, correction of which may have facilitated treatment.

Obviously a one-subject trial can only suggest ideas for further exploration, since it is impossible to separate idiosyncratic factors from the total response. However, it seems that the many approaches to an allergy-schizophrenia connection vary among themselves, and none take the present view, exploring the depletion aspects of a nearly constant high immune response, or tracing this to a possible nitrogen/niacin abnormality.

The present theory could dispense with the words "allergy" and "schizophrenia", substituting the word "starvation"—or less dramatically, "depletion". It redefines the word "autoantibody" as a depleted and abnormal antibody.

It also offers some hope of avoiding the "avoidance" therapy in treatment of allergies, suggesting that if the integrity of the body's organs is restored, the "allergic" sensitivities may no longer exist.

In sum, it suggests that the magnitude of a prolonged immune system response is capable of draining the system from brain to bunions, creating potentially innumerable problems, the nature of which may someday be predicted by a study of individual genetic heritage. To paraphase, "One man's rheumatism is another man's psychosis."

Discussion

In the present study, the tryptophan amino acid pathway is implicated in atopic allergy and schizophrenia, with nitrogen depletion creating a condition of relative niacin starvation.

The tryptophan and tyrosine pathways, linked through feedback mechanisms (Melt-zer, 1979, pages 114, 115, 185) (Fig. I), are thought to produce abnormal feedback as a factor in the schizophrenic condition, in combination with immune system abnormalities accrued through deficiency.

An initial infection, either acute or mild but prolonged, may trigger the initial depletion of somatic nitrogen in this genetic type, to a point where it cannot be restored by ordinary dietary intake, or will be restored only gradually under optimum dietary and health conditions.

It is suggested that the nitrogen loss affects a proper rate of nicotinic acid metabolism; that this in turn may weaken the integrity of molecular cell structure in vulnerable areas of the system, rendering it susceptible to invasion by other environmental substances as nitrogen is drawn from vital areas to meet immune defense needs; that very real invasions by certain environmental substances, to which the individual is otherwise naturally immune, become possible; that this will require a still greater immune response; and that the system is thus further depleted and a vicious circle established with a downward spiral into atopic allergy, complete with abnormal sensitivity in skin, respiratory and perhaps gastrointestinal organs. Other conditions may then develop as well, depending upon genetic and idiosyncratic metabolic factors.

Powanda (1977) observes that the defense system can be overwhelmed, increasing susceptibility to infection, in some cases by organisms normally classified as non-pathogenic.

In the presence *of* old or newly established "allergens", the conditions may worsen under an increasing drain of niacin or possibly other amino acids.

Niacin's participation as a co-enzyme may make large quantities of this factor necessary in controlling and finally healing the proposed deficiency-induced damage. While enzymes are used and reused unchanged in metabolic reactions, and thereby are necessary only in limited quantities in ordinary life-support processes, it would seem logical to suppose they would be necessary immediately and in large quantities where immune system production is underway in direct response to the sudden presence of invasive substances. An immune system response may be immense and immediate, and for the healing processes to proceed ahead of the deficiency and immediate drain, more niacin might be essential, if it is a key source of nitrogen in this

proposed syndrome. Available nutrients, after all, do not appear by magical means.

Niacin as a water-soluble vitamin is disposed of by the body when unneeded, thus probably breaking up NAD factors and rendering them unavailable when the next large scale exposure to allergens or infectious agents is met. A new and large supply of niacin might then again be needed, although this area has not been well explored. Heg-stad (1978) points out that in most exploration of the inborn errors of metabolism of amino acids, the adverse effects of excessive intake have been the focus, rather than abnormalities which result in higher requirements.

Depleted resources affecting host defense might account for the "abnormal lymphocyte" found in schizophrenia (Fessel et al., 1965) and for the higher than normal IgE production in atopic allergies, which implicates the complement system, since IgE is the only immunoglobulin which does not require interaction with complement for its function.

The variability of possible idiosyncratic depletion may account for much of the confusion encountered when efforts are made to pinpoint basic defects responsible for either atopic allergies or schizophrenia. A complement-lupus-schizophrenia correlation is intriguing, for example (Schur, 1978).

Depleted immune system resources may account for both the schizophrenic and atopic allergy conditions if the following possibility is considered:

Venter et al. (1980) have proposed that an autoantibody to the beta-2-adrenergic receptor is present in individuals with asthma and allergic rhinitis. The present paper proposes that this so-called autoantibody is the product *of* deficiency-motivated metabolic irregularity which diminishes transport *of* epinephrine to the respiratory system in a situation of high immune activity—a situation in which additional epinephrine to the respiratory areas is desirable, but where such suffusion body-wide could be disastrous.

This paper further proposes that this hypothesized beta-2-adrenergic receptor autoantibody is one of the many abnormal immune agents and other cells which may be created by dwindling availability of nitrogen in key areas; yet when and if this autoantibody fails to be produced under these conditions, it may create the schizophrenic or other thought/behavior disturbance by suffusion of noradrenalin in the brain. Dopamine or other metabolites might be similarly affected in other cases.

The epinephrine response, probably always in a state of relative excess under high immunity conditions (unless it too becomes depleted) then is free to irradiate the respiratory system; the lungs are relaxed, there is no sneezing or inflammation—and the brain is steadily suffused with an excess of the substance, with resulting over-stimulation and chaotic sensory input.

Probable fluctuating levels of serotonin through overdrain of tryptophan on the pyrrolase pathway and erratic tryptophan/tyrosine feedback might also affect the brain's neurotransmission and screening efficiency in this syndrome, allowing random input of inappropriate material.

The fact that norepinephrine is credited for focusing attention in the brain's reticular activating system should be considered significant. It can be surmised that continuing excesses would allow too much intrusion of sensory data, perhaps from memory and imagination as well as from environmental and somatic sources, thereby producing the various degrees of thought-intrusion, confusion and eventual hallucination.

The schizophrenic may have attained a vital balance at a new level-and is overdosed on his own thought-potentiates.

Since atopic allergies and schizophrenia have been considered negatively correlated, it seems probable that the tendency to form or not form Venter's proposed autoantibodies to the beta-2-adrenergic receptor may be determined by another genetic idio-syncracy operating in combination with the tryptophan-niacin irregularity proposed here. The present theory supposes, however, that the niacin metabolic irregularity and nitrogen depletion is basic to both conditions; allergies and thought/behavior disturbances, as found in families evidencing both pathologies in different individuals It seems certain that this proposed

deficiency could account for many sub-clinical conditions of either allergy or thought/behavior irregularities. Obvious confusional states would not be manifest unless and until the condition of depletion became extreme.

Serotonin treatment for allergies, and that based on the biogenic amine hypothesis for schizophrenia, may have erred in supplying only serotonin on the tryptophan sequence, when it was niacin on the tryptophan-pyrro-lase pathway which was acutely needed. Niacin, it can be theorized, would have filled a distinct need, since the metabolic abnormality may be on the tryptophan-pyrrolase-nicotinic acid pathway.

Meanwhile, the schizophrenic metabolic phenomena described by Gilka (1975) might be as well explained by a heavy immune system drain as by Gilka's proposed enzyme blocks.

Gilka points out that an excess of serotonin inhibits tryptophan pyrrolase. The present theory suggests that the condition of serotonin excess may be the result of high production of noradrenalin (Figure 1).

Incorporating Gilka's proposal into Figure 1, we have an excess of noradrenalin activating tryptophan hydroxylase on the serotonin pathway, and the excess serotonin inhibiting pyrrolase activity and subsequently decreasing nicotinic acid production.

Working this system in reverse implies that a heavy immune system drain on the pyrrolase pathway, calling for niacin either as a regulatory coenzyme or in actual synthesis of protein for immune agents, may deplete dietary tryptophan/nitrogen to force a situation of pyrrolase inactivity with a tendency toward activation of tryptophan hydroxylase and then noradrenalin, possibly permitting spillover into closely-related adrenalin to subdue dangerous immune system over-drain and prevent anaphylactic shock.

—But the excessive noradrenalin production would again activate tryptophan hydroxylase, increase serotonin and further inhibit tryptophan pyrrolase. The unnatural interplay of these regulatory feedback mechanisms under depletion conditions might create the chronically depressed pyrrolase function noticed by Gilka, and possibly create an overavailability of noradrenalin on the tyrosine pathway in genetically susceptible individuals.

In spite of increasingly inferior host defense in some areas as a result of this proposed syndrome, the near-constant immune surveillance established by the presence of invading "allergens" may render afflicted individuals safer in some other respects, providing a suggested "survival value" which has been proposed in both allergies and schizophrenia, although evidence is conflicting. Some researchers have found a negative association of both conditions with cancer, for instance (Ure, 1969; Rassidakis, 1973).

Four ways are suggested in which allergic or schizophrenic individuals might become depleted in nitrogen resources, with resulting immune system starvation. In each case, severe or prolonged infection might well be a precipitating factor. Genetically, this individual:

1. May be incapable of metabolizing sufficient niacin to cope with ordinary defense needs and therefore constantly lose a little ground until a significant deficiency has accrued.
2. May have an impairment in native immunity elsewhere in the system, requiring unusually high compensatory production of immune agents and creating a constant drain on nitrogen/niacin.
3. May be subject to easier-than-normal loss of nitrogen during illness or other stress due to a genetic nitrogen bonding defect on the tryptophan/niacin pathway.
4. May possess a genetically superior ability to mount an immune defense, thereby requiring more dietary nutrient intake than the individual can obtain, tolerate, or is in the habit of consuming; thereby also creating a constant relative net loss of nitrogen/ niacin.

Any or all of these proposals may be involved in different individuals. However, consideration No. 4 is interesting, not only because it presupposes that the "schizophrenic taint" may actually be based in a superior but starving immune system, but also because it would help account for the "survival value" of the trait, mentioned above.

It also seems likely that an above-normal defense potential, maintained at low levels by dietary limits, might be nearly impossible for researchers in pathology to detect, accustomed as they are to looking for defects, not favorable mutations.

By supplying nicotinic acid to these individuals, the body may be able to regain a stability it otherwise lacks. As the pathogenic sensitivities clear, smaller amounts of this supplement will probably be sufficient.

As a metabolite, niacin is probably quite safe, avoiding certain side effects and risks of traditional allergy treatment, although its long range effects cannot be stated here. Powanda (1977) suggests the therapeutic administration of amino acids or other readily available sources of metabolizable nitrogen to aid host defenses.

It would seem that critics of the niacin therapy for schizophrenia may have been hasty in their rejection of the substance on the basis of its superficial effects, failing to realize that rashes and other nuisance phenomena are typical of the body's efforts to heal. Powanda (1977) refers to the neglect of the anabolic facets of infection in early studies, and adds that the magnitude of this response is surprisingly large.

Total medication charts from the present trial of niacin for an allergic subject show the high niacin dosage coupled with high need for topical cortisone during the period of healing in the eczema-afflicted areas (Fig. II, 1979), compared with usage after the healing of these areas was complete, when niacin use was reduced and there was zero use of topical cortisone.

Cautions

Large doses of "high immunity" niacin administered too abruptly to allergic subjects may precipitate shock-like reactions as too much defense artillery is suddenly mobilized. Painful dermatitis, inflammation in allergy-afflicted areas both internal and external, high liver enzyme production and other symptoms of violent healing effects may develop.

It is possible that administration of corticosteroids simultaneously with niacin might avert some of these problems, as seemed to have occurred in the case of eczema treated with topical cortisone in the present trial.

Niacin dosage must be built up gradually and the subject observed and questioned closely for developing problems as the immune system begins to cope with what may be years of accumulated damage. This effect may be intensified in subjects with poor nutrition, those who have used traditional allergy treatments for long periods of time, or the elderly.

A better back-up program of other amino acids and related metabolites, vitamins, minerals and proteins should be developed to facilitate healing and perhaps avoid some of the treatment-induced discomforts. New means of determining these needs are constantly being found (Baker et al., 1981).

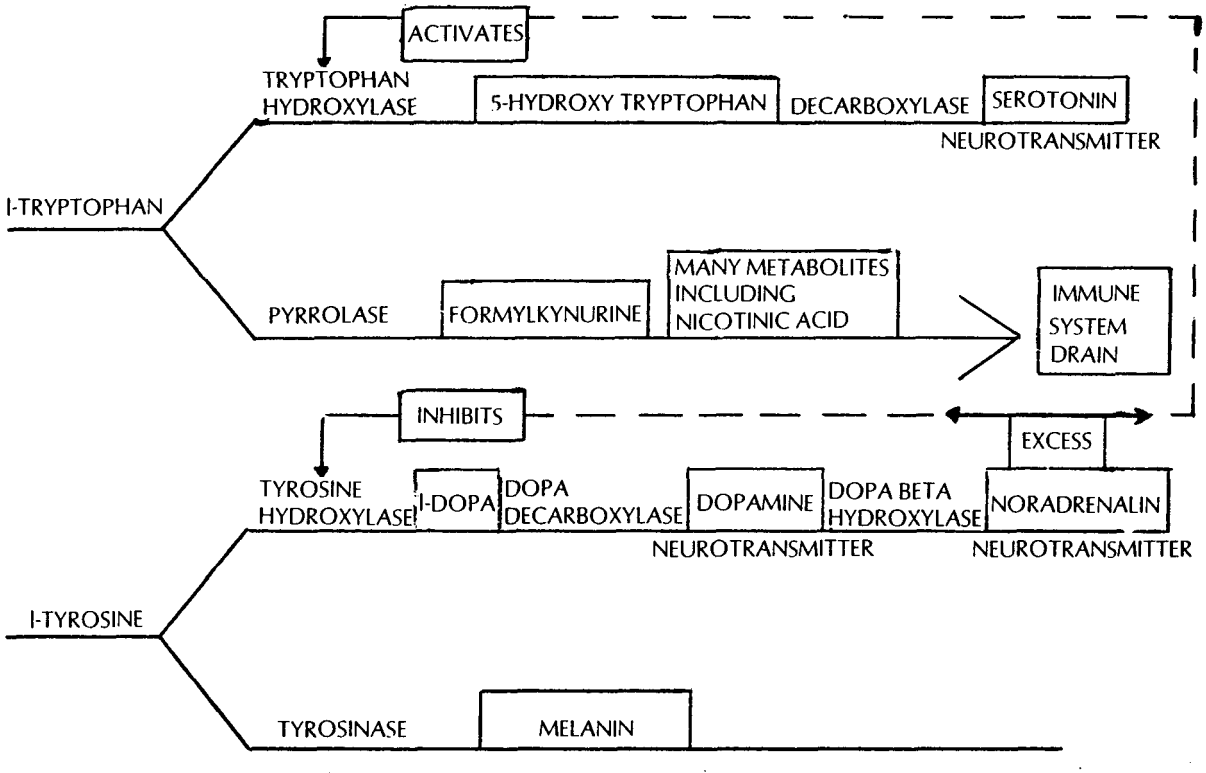
Further Research

Future research should certainly include a review of case histories establishing the presence of atopic allergies and mental disturbances, including hyperirritability, delinquency and criminal behavior, in different individuals in the same families. While this study could not obtain such histories, it was called to the author's attention that several other families in the immediate vicinity do seem to contain this pattern.

A further review of the literature should be made with these correlations and the nutrient approach in mind.

Further trial of niacin should be made in both the allergic and behavior-affected members of families conforming to this proposed syndrome.

FIGURE 1



TRYPTOPHAN-TYROSINE METABOLIC PATHWAYS WITH PROPOSED IMMUNE SYSTEM "DRAIN"

FIGURE II - ALLERGY MEDICATIONS PURCHASE/USE RECORD

YEAR	ASTHMA	ALLERGIC RHINITIS	ECZEMA	INJECTIONS (all allergy)	COUGH	INFECTIONS	NIACIN
1969 1972		unk. NP	....	....	....	....	....
1973	unk. NP	unk. NP 60 Copyronil	—	—	—	—	—
1974	unk. NP 24 Marax	420 Copyronil	4 oz. Kenalog	—	8 oz. Phen.	40 Penicillin VK	—
1975	96 Marax unk. NP 50 Brethine	510 Copyronil 15 Teldrine unk. Triten	8 oz. Kenalog	120 mg Dep.	16 oz. Phen.	40 Actifed 3.5 g Neo-sporin	....
1976	856 Marax sample inhale	562 Copyronil	12 oz. Kenalog	60 mg Kenalog .3 susphrine 40 mg. Dep.	32 oz. Phen.	44 Ampicillin	....
1977	432 Marax 150 Aminoph. 30 cc D-M	510 Copyronil	20 oz. Kenalog	180 mg Kenalog	28 oz. Phen.	10 cc Gara-mycin 12 V-cillin-K	
1978	1,140 Aminoph.	540 Copyronil 2 Dec. Turb. 40 Benadryl	20 oz. Kenalog 4 oz. Hydroc.	....	8 oz. Phen. unk. NP (Rob)	160 Ampicillin 60 g Eurox cr	....
1979	162 Aminoph.	1 Dec. Turb. 60 Copyronil	26 oz. Kenalog 2 oz. Hydroc.	—	unk. NP (Rob)	40 Tetracycline	735 g + 24.8 g ncmd.
1980	300 Aminoph.	60 Copyronil	—	—	unk. NP (Rob)	unk. Neospor. unk. Garamyc. 44 Ampicillin	444 g + 25.4 g ncmd.
1981 (1st 6 mos)	180 Aminoph..		....	....	....	30 Ampicillin	150 g + 25.4 g nmcd.

Figures for medications are purchase records obtained from the subject's pharmacists, clinic and hospital, except in the case of niacin and niacinamide, which are actual use through April 1980, and consist of purchase records for prescriptions beyond that point.

KEY FOR FIGURE II

ABBREVIATIONS:
Aminoph. - Aminophyllin 200 mg tabs
Dec. Turb. - Decadron Turbinaire
D-M - Duo Medihaler
Dep. - Depomedrol
Garamyc. - Garamycin Ophthalmic ointment.
Hydroc. - Hydrocortisone 1% cream
ncmd. - Niacinamide in multi-vitamin tabs
NP - Non-Prescription
Phen. - Phenergan with codeine
Rob. - Robitussin expectorant
unk. - Unknown
STRENGTH
Ampicillin 250 mg caps
Aminophyllin 200 mg tabs
Benadryl 25 mg caps
Hydrocortisone 1% cream
Kenalog 1% cream
Neosporin eye drops
Penicillin VK - 250 mg caps Tetracycline - 250 mg caps Triten 25 mg Teldrine 12 mg

References

AMERICAN PSYCHIATRIC ASSN.: Megavitamin and Orthomolecular Therapy in Psychiatry. APA Task Force Report, Book 7, July, 1973.

BAKER, H. and FRANK, O.: A Vitamin Profile of Metabolic Disturbances. J. Applied Nutr. 3, 3-15, Spring, 1981.

BALDWIN, J.A.: Schizophrenia and Physical Disease (Editorial). Psychological Med. 9, 611-618, Nov. 1979.

BEUMER, H.M.: Pirbuterol in the Treatment of Bronchial Asthma. Int. J. Clinical Pharmacol. Biopharm. 17, 18-25, January, 1979.

BULL, H.G., FERRAZ, J.P. and CORDES. E.H.: Concerning the Mechanism of the Enzymatic and Non-Enzymatic Hydrolysis of Nicotinamide and Nucleotide Coenzymes. J. Biol. Chem. 253, 5186-5192, July, 1978.

CARR, R.I., SHUCARD, D.W., HOFFMAN, S.A., HOFFMAN, A.W., BARDANA, E.J. and HARBECK, R.J.: Neuropsychiatric Involvement in Systemic Lupus Erythematosus. Birth Defects 14, 5, 209-235,1978.

CHYREK-BOROWSKA, S., GRUSZECKA, M. and HOFMAN, J.: A Trial of Combined Treatment With Hypo-stamine and Nicotinamide of Allergic Reactions and Bronchial Asthma. Pol Tyg Lek 33, 3,1978.

FALKO, J.M., WILLIAMS, J.C., HARVEY, D.G., WEIDMAN, S.W., SCHONFELD, G. and DODSON, W.E.: Hyperlipoproteinemia and Multifocal Neurologic Dysfunction in Systemic Lupus Erythematosus. J. Pediatr. 95, 4, 523-529, October, 1979.

FESSEL, W.J., HIRATA-HIBI, M. and SHAPIRO, I.M.: Genetic and Stress Factors Affecting the Abnormal Lymphocyte in Schizophrenia. J. Psych. Research 3, 275-283, 1965.

GATTAZ, W.F. and BECKMANN, H.: HLA Antigens and Schizophrenia. Lancet 1, 98-99, Jan. 12,1980.

GILKA, L.: Schizophrenia: A Disorder of Tryptophan Metabolism. Acta Psych. Scand., Supplement No. 258, 1975.

HARIK, S.I., LA MANNA, J.C., LIGHT, R.I. and ROSENTHAL, M.: Cerebral Norepinephrine: Influence on Cortical Oxidative Metabolism in situ. Science 206, 69, Oct. 5, 1979.

HEGSTAD, D.M.: Assessment of Nitrogen Requirements. Am. J. Clin. Nutr. 31,1669-1677, Sept. 1978.

HOFFER, A.: Treatment of Schizophrenia. Pp. 83-89. In: Williams, R.J. and Kalita, D.K., (eds.): A Physician's Handbook on Orthomolecular Psychiatry, New York, Pergamon Press, 1977.

HOFFER, A. and OSMOND, H.: How to Live with Schizophrenia. University Books, 1966.

JAUS, H., STURM, C., GRASSLE, B., ROMEN, W. and SIEBERT, G.: Metabolic Effects and Liver Damage After Prolonged Administration of High Doses of Nicotinamide to Rats. Nutr. Metab. 21, Supplement 1, 35-41, 1977.

KALLMAN, F.J.: The Genetics of Schizophrenia. J.J. Aug-ustin Co., 1938.

LABADARIOS, D., McKENZIE, D.Y., DICKERSON, J.W.T. and PARKE, D.V.: Metabolic Abnormalities of Tryptophan and Nicotinic Acid in Patients with Rheumatoid Arthritis. Rheumatol. Rehabil. 17, 227-232, November, 1978.

LEE, T. and SEEMAN, P.: Elevation of Brain Neuroleptic/ Dopamine Receptors in Schizophrenia. Am. J. Psychiatry 137,191-197, February, 1980.

LEWIS, A.: The Psychoses. P. 1763. In: Beeson, P.B., McDermott, W., and Wyngaarden, J.B. (eds.): Cecil Textbook of Medicine, Philadelphia, W.B. Saunders Co., 1963.

MATHE, A.A., WIESEL, F.A., SEDVALL, G. and NYBACK, H.: Increased Content of Immunoreactive Prostaglandin E in Cerebrospinal Fluid of Patients with Schizophrenia. Lancet 1,16-18, Jan. 5,1980.

MELTZER, H.L.: The Chemistry of Human Behavior. Nelson-Hall, 1979.

MISUR, M., and TAKAO, M.: Allergic Cerebral Manifestations in a Patient with Bird Breeder's Lung. Ann. of Allergy 41,176-178, September, 1978.

MOLCAN, J. et al.: Preliminary Experiences with Nicotinamide Administration in Schizophrenia (Author's Translation). Bratisl. Lek. Listy. 69, 553-556, May, 1978

NEWBOLD, HI., PHILPOTT, W.H. and MANDELL, M.: Psychiatric Syndromes Produced by Allergies: Ecolo-gic Mental Illness. J. of Ortho. Psychiatry 2, 3, 1-9, 1973.

PAULING, L.: Treating Mental Disorders (letter). Science 206, 404, October 26,1979.

PHILPOTT, W.H.: Immunological Deficiencies in Schizophrenia. In: Williams, R.J. and Kalita, D.K., (eds.): A Physician's Handbook on Orthomolecular Psychiatry, New York, Pergamon Press, 1977.

POWANDA, M.C.: Changes in Body Balances of Nitrogen and Other Key Nutrients: Description and Underlying Mechanism. Am. J. Clin. Nutr. 30, 1254-1268, August, 1977.

RASSIDAKIS, N.C. et al.: On the Incidence of Malig nancy Among Schizophrenic Patients. Agressologie 14, 269-273, 1973.

REA, W.J., BELL, I.R., SUITS, C.W. and SMILEY, R.E.: Food and Chemical Susceptibility After Environmental Chemical Overexposure: Case Histories. Annals of Allergy 41, 2,101-110, August, 1978.

REA, W.J.: Environmentally Triggered Cardiac Disease. (Unpub.). Supported by the Human Ecology Research Foundation of the Southwest.

RUDIN, D.O.: Covert Transport Dysfunction in the Choroid Plexus as a Possible Cause of Schizophrenia. Schizophr. Bull. 5, 4, 623-626,1979.

SCHUR, P.H.: Genetics of Complement Deficiencies Associated with Lupus-like Syndromes. Arthritis Rheum. 21, S153-160 (supplement), January, 1978.

SCRIMSHAW, N.S.: Diseases of Nutrition, Ch. 470, pp. 1678-1680. In: Beeson, P.B., McDermott, W. and Wyngaarden, J.B. (eds.): Cecil Textbook of Medicine, Philadelphia, W.B. Saunders Co., 1979.

STAMLER, J.: The Coronary Drug Project—Findings with Regard to Estrogen, Dextrothyroxine, Clofibrate and Niacin. Adv. Exp. Med. Biol. 82, 52-75, 1977. (Coronary Drug Project Research Croup.)

TURLAPATY, P. and ALTURA, B.: Magnesium Deficiency Produces Spasms of Coronary Arteries: Relationship to Etiology of Sudden Death Ischemic Heart Disease. Science 208,198-200, April 11,1980.

URE, D.M.J.: A Negative Association Between Cancer and Allergies. Scot. Med. J. 14, 51-54,1969.

U.S. DEPT. H.E.W.: Immunology: Its Role in Disease and Health—Summary Report of the Task Force on Immunology and Disease, U.S. Dept. of Health, Education and Welfare Publication No. (NIH) 77-940,1976.

U.S. DEPT. H.E.W.: Asthma and the Other Allergic Dis-eases-NIAID Task Force Report, U.S. Dept. of Health, Education and Welfare, National Institutes of Health, 1979.

VENTER, J.C., FRASER, CM. and HARRISON, L.C.: Auto-antibodies to Beta-2-Adrenergic Receptors: A Possible Cause of Adrenergic Hyporesponsiveness in Allergic Rhinitis and Asthma. Science 207, 1361-1363, March 21, 1980.

WILSON, CO. and GISVOLD, O. (eds.): Textbook of Organic, Medicinal and Pharmaceutical Chemistry, 3rd Edition. J.B. Lippincott Co., 1956.