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Controversy in Allergy

Neurologic Allergy

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Introduction

Perhaps no area in allergy arouses such passions as the idea that allergic mechanisms adversely affect the nervous system. At one point in my professional life, it would have been impossible to write a review without a strong position supporting or denying the clinical claims of a fringe group of physicians.

Now I believe that a sober review can dispassionately examine this area. There are several important caveats. Much of the newer information is derived from work in animals or in human brain slices in vitro. There are sometimes paradoxical differences among animals in their cerebral responses to such mediators as histamine. Brain slices are useful tools, but exist outside of the complex organism called a human being. Many important modulatory steps may be missed when the tree is no longer in the forest.

In spite of these caveats, I believe most readers will find information that is truly new and exciting to them. It is possible that their thinking will be stretched and old dogma reevaluated.

At the very least, in this era of psychoneuroimmunology, the interactions, if any, between the nervous system and allergy can be evaluated by competent investigators. Facts will eventually alter opinions, if they come from objective replicated studies.

The clinical observation will follow the basic science review. The specific clinical disorders addressed are:

1. Epilepsy, fits and convulsions;
2. Attention deficit syndrome, childhood hyperactivity, hyperkinetic syndrome;

3. Tension–fatigue syndrome and allergic toxemia;
4. Ménière's syndrome, vertigo with fluctuating hearing loss;
5. Peripheral neuropathy;
6. Multiple sclerosis;
7. Psychiatric disorders;
8. Left-handedness and allergic disorders; and
9. The *Candida* syndrome.

Background

We may lay the blame for the original sin in neurological allergy affecting our present knowledge on Charles Blackley. He is the founding father of neuroallergic ideas. Blackley is chiefly remembered for his work proving that pollen caused hay fever. He suffered severe hay fever symptoms. He was the volunteer subject for his famous studies.

Pollen inhalation challenges caused the respiratory symptoms of hay fever and asthma. After these challenges, Blackley was listless, restless, and suffered insomnia. These symptoms were not present prior to challenge and waned when challenges were stopped *(1)*. Sadly, most of us learn of Blackley's studies from our teachers, and never get to review the entire gamut of his observations.

Blackley's contemporary, Dr. Fort, described a patient whose fits were reproducibly provoked by eating beans *(2)*. The search for allergic mechanisms in epilepsy began with this 19th-century report.

As the 20-century began, the excitement caused by the description of anaphylaxis stimulated investigator to seek anaphylactic mechanisms for any and all idiopathic disorders *(3)*. This shotgun approach may seem foolish in retrospect; however, almost a century later, it must be viewed in light of the relative paucity of scientific medical knowledge at the time. The germ theory of infectious disease was only a quarter of a century old.

None of the clinicians who provided the observations that I will later describe had either the support of molecular biology or the ability to accurately measure mediator changes. None of them had heard of IgE, the complement cascade, cytokines, and so on. At this point, I wish to provide the reader the benefit of this basic research information, before he or she examines the clinical reports.

Newer Research Findings in the Central Nervous System with Potential Applications to Neuroallergic Investigations

Once more, I must caution the reader to remember that there are important species differences in central nervous system (CNS)

reactions. A rat or cat brain may not be an adequate model for a human brain. Likewise, human brain-slice-incubation studies, although elegant, may have many deficiencies, as noted above, as they are performed in ex vivo states.

The greatest intellectual barrier to accepting that peripherally generated allergic events and mediators could affect cerebral function is a physicochemical barrier, the "blood–brain barrier." In the simplest schema, only lipophilic molecules pass freely from the peripheral blood into the brain. Lipophobic molecules are excluded or restricted by the specialized vascular endothelium. Movement of these molecules into the brain requires an active transport system.

A number of investigators working with animal models have found that the blood–brain barrier is vulnerable to breakdown in the presence of mediators. Studies in rodents have demonstrated that histamine, prostaglandins, bradykinin, and platelet-activating factors decrease the blood–brain barrier's exclusionary properties *(4)*.

Similar investigations have not yet been done in humans. However, immune-complex diseases can deposit large protein molecules (the complexes) in brain tissue. In humans with systemic lupus erythematosus (SLE), the choroid plexus is preferentially affected *(5)*.

Recognized CNS Activities of Mediators, Which Can Be Derived from Allergic Reactions

Histamine H-1, H-2, and H-3 Receptors

In recent years, histamine's role as one of the important basic CNS mediators is becoming more appreciated. There is a distinct histaminergic nervous system within the brain. Cerebral histamine, under normal circumstances, is synthesized and secreted by neurons in the hypothalamus. The brain contains the enzyme histidine decarboxylase to transform histidine from external dietary sources to histamine. Pyridoxal phosphate is a critical cofactor. Histamine is degraded by the enzymes diamine oxidase and imidazole-*N* methyl transferase *(6)*.

Perivascular mast cells in the brain contain histamine *(7)*. H-1 and H-2 histamine receptors occur in an arrangement similar to that found in other organs *(7)*. There is also a recently described H-3 receptor *(8)*.

The H-1 receptor when activated causes uptake of noradrenalin and serotonin by brain slices *(9)*. Histamine via an H-1 activity causes stimulatory or arousal behavior in intact cats *(10)*.

Swimming despair in rats is used as a model to study depressive illness. Histamine by an H-2 receptor action causes swim-

ming despair to appear in rats. H-2 antagonists causes relief of the actions in the rat model *(11)*.

Histamine appears to regulate its own release from peripheral cells by an H-2 mechanism. Autoregulation of histamine release also occurs in the human brain. Inhibitory signals come from H-3 receptors *(12)*.

Increasing the diet concentration of histidine, the precursor of histamine, increases the brain concentration of histamine. Supplements of pyridoxine markedly increase how much any given level of histidine increases brain histamine concentrations. Pyridoxine will increase CNS histamine when there is no diet alteration. The effects of B-6 on tryptophan, the precursor of serotonin in the brain, are the same as with histidine *(13)*. B-6 has been used with variable success in treating human depression.

The tricyclic antihistamines with powerful H-1 antagonism are useful in the clinical management of depressive illness. It is unclear whether they affect H-3 receptors. Some of the tricyclics have demonstrated anti-H-2 receptor activity.

Histamine applied to brain tissue can alter a normal EEG *(14)*. It will increase the frequency of electrical spikes in nervous tissue *(15)*.

Seventy years ago, the pioneer investigators Van Leeuwen and Zeydner *(16)*, reported that patients with epilepsy, migraine, asthma, or atopic dermatitis shared a serum abnormality not found in normals. Some of these patients' blood contained a spasmogenic activity. Judged by its rapid action in contracting guinea pig ileum, this was most likely histamine. More recent investigations have shown increased plasma histamine levels in migraineurs, which increase during an attack. Spontaneous release of histamine from basophils is increased in migraineurs. This abnormality occurs in other allergic disorders *(17,18)*.

Parenteral histamine given to normal humans causes a variety of behavioral changes from stimulation to sedation. There is an intersubject as well as dose-response variation to the quality of these responses. One almost always occurring effect is throbbing headache. The dose-response curve for migraineurs is shifted to the left, as might be expected *(19)*.

Serotonin

Serotonin is a very important mediator of CNS activity. Two percent of the entire body store of serotonin is found in the brain and the CNS. For comparison, 8% of total body serotonin is passively taken up by platelets. Ninety percent is found in the enterochromaffin cells of the intestine *(20)*. Investigators have found a pe-

ripheral defect in serotonin uptake by platelets in asthmatics and migraineurs. No comparable studies of intracerebral serotonin abnormalities have been done. Serotonin is found in rat mast cells, but not in human mast cells or basophils.

Serotonin has a large number of normal activities in the CNS. These include effects on appetite, sleep, and mood. Serotonin regulates the number of low affinity beta adrenergic receptors in the brain *(21)*. Serotonin is involved in the sensation of anxiety, and the various clinical anxiety disorder in human beings *(22)*. There are at least five to six distinct receptor sites for serotonin in the brain *(23)*.

Usually, serotonin within the CNS is synthesized by neurons especially of the hypothalamus. Increased dietary levels of Tryptophan with or without pyridoxine will increase brain serotonin levels *(13)*. However, it is likely that massive release of serotonin from platelets, as in a migraine attack, stimulated by platelet-activating factor, can cause increased serotonin levels in the CNS *(24)*.

Prostaglandins and Leukotrienes

Animal studies have shown that prostaglandins, but not leukotrienes, are involved in causing cerebral edema. Leukocytes found intracerebrally, including basophils, are the source of intracerebral leukotrienes. Less is known of the role of intracerebral leukotrienes in humans. Prostaglandin D is released and leukotrienes are generated during type I hypersensitivity reactions as well as by cerebral ischemia *(24,25)*. Many early clinical reports of food-induced brain-derived symptoms stressed that acute transient cerebral edema occurred. The cerebral edema was thought to play some role in the disease reaction *(26)*. Prostaglandin D, like histamine, can alter the blood–brain barrier. Both can cause cerebral edema in animal models *(27)*. The effect of prostaglandins and arachidonic acid in causing cerebral edema is found in rodents, but not in cats. There are no studies in humans to give us information about the possible relevance.

Prostaglandin E2 in the CNS causes hypalgesia and antagonizes both natural opioids and morphine. The α-adrenergic antagonists phentolamine blocks this effect *(28)*. The same prostaglandin E2 injected peripherally causes a short-lived migraine-like attack *(29)*.

Bradykinin

Bradykinin is a mediator that has been of interest to allergy researchers. When bradykinin is injected subcutaneously, it produces pain and erythema. Application to the CNSs excites those

sensory neurons associated with pain and causes a state of hyperalgesia *(30)*. The same cerebral application amplifies the inflammatory response of carrageenan-induced paw edema in rats *(31)*. Bradykinin can also break down the endothelial blood–brain barrier *(32)*.

Platelet-Activating Factor (PAF)

The importance of PAF acether in human allergic disease is becoming increasingly appreciated. PAF acether is synthesized in the brain. The level of PAF is elevated during convulsions. PAF injected peripherally causes increased vascular permeability and breakdown of the blood–brain barrier *(33)*. There appears to be an increase in activated platelets, with a decreased response to exogenous PAF in such disorders as migraine *(34)*.

The Immune Response Within the CNS

Normally the blood–brain barrier excludes immunoglobulin from entering the brain *(35)*. Immune-complex disorders, such as SLE, alter this state, perhaps through complement activation. The choroid plexus is the most common site for the immune complexes to be deposited *(36)*. Increased vascular permeability results from histamine and other mediators released by C3a and C5a *(37)*.

Animal models may differ significantly from humans. Large macromolecules are able to penetrate the blood–brain barrier in normal untreated rats. Radiolabeled IgG, hemoglobin, or α gliadin appeared in the brain of rats after they were injected. It appears that immunoreactive proteins of considerable size can be found in brain tissue *(38)*. Clearly the blood–brain barrier is not as complete as once thought. Exclusion of large macromolecules may be species dependent and involve special mechanisms.

The sum of our present knowledge raises the possibility that antibody and antigen (allergen) interaction can occur within the CNS. It also appears that a significant amount of mediator released from a peripheral response may be able to alter the blood–brain barrier and secondarily allow the mediators to affect the CNS.

Mediator-Containing Cells in the CNS

Mast cells of the CNS reside in the perivascular connective tissue. They are not found in the brain parenchyma. They are also found in nerve sheaths *(39)*. Basophils circulate through the brain in the blood along with other granulocytes.

The facts that we presently know allow the possibility of allergic reactions within the brain and affecting the brain. The model of

a mast cell or basophil with specific IgE antibody on its surface can occur within the cerebral vasculature and affect the brain itself through the release of allergic mediators. Whether this really occurs in humans and whether it is of clinical consequence in some or any patient remains to be proven.

Clinical Observations of Allergy Affecting the Nervous System

Epilepsy

Migraine and epilepsy have been linked as disorders by many authors *(40,41)*. Epileptics were reported to have the same spasmogenic substance in their blood as asthmatics, migraineurs, and patients with atopic eczema *(16)*.

Early neurologists, such as Foster Kennedy, described convulsions caused by presumed food allergy *(42–44)*. Dr. Kennedy stated that he had personally observed many cases of food-allergy-induced acute transient edema of the optic nerve and retina *(44)*.

The initial mechanisms suggested for food-induced convulsions were based on observations of the cerebral tissues of patients with serum sickness. One patient with a horse-serum reaction underwent craniotomy. He was aphasic and hemiplegic. He suffered generalized urticaria. The craniotomy findings were hyperemic swelling of the brain *(45)*.

Paganiez, a pioneer in allergic investigation, purposefully rechallenged a patient who was suspected to have food-induced epilepsy. The challenge provoked a seizure *(46)*. Since this time, there have been over 75 reports of food-induced seizures.

Early investigations first sought to find whether allergic disease was increased among patients with fits. Ward and Patterson studied 1000 hospitalized epileptic patients at two long-term residential facilities *(47)*. They used 100 normals as their control population. They tested the subjects with 64–72 scratch food skin tests. The rate of sensitization to one or more food proteins was 37% in one hospital's patients and 67% in the other facility's epileptics. The comparable rate was 8% for the control group *(47)*.

A similar study was performed by Wallis, Nichols, and Craig. Thirty-eight percent of epileptic subjects reacted to one or more allergen. Only 4% of the control population reacted positively *(48)*. The speculation was that allergy sensitization provoked some seizures and that allergic management could decrease seizure frequency and severity.

Dr. Susan Dees tested this hypothesis by treating 22 epileptic patients who also were allergic *(49)*. She used a combination of desensitization, avoidance measures, and antiallergic medications. Decreased epileptic problems occurred in 18 of 22 epileptic children. In fact, of the 20 patients taking anticonvulsants, 9 were able to stop the medications. As a control group, she followed 15 nonallergic epileptic children. Only 1 of the 15 were able to discontinue drug therapy. There were only minimal changes in the clinical status of these patients *(49)*.

Egger et al., in a more recent study, reported that a special diet could decrease fits in children *(50)*. The study involved 63 children with epilepsy. The children ate an oligoantigenic or restricted diet consisting of one meat, one grain, one vegetable, and so forth.

Forty-five of the epileptic children also suffered from migraine or hyperactivity. Epilepsy alone was seen in 18 children. Twenty-five subjects became seizure free. Eleven others improved. All of these subjects had epilepsy plus migraine or hyperactivity. None of the 18 patients who had only epilepsy improved on the diet.

The diet was followed by a reintroduction phase and the return of seizures. Based on the responses during the reintroduction phase, 16 subjects underwent placebo-controlled blinded food challenges. Eight of the 16 had seizures with one or more food challenges. No seizures occurred with placebo challenges.

By way of comment, it is most interesting to speculate how migraine and epilepsy are related as allergic disorders. Common migraine involves extracerebral intracranial vessels. There is strong evidence (*see* Vaughan's article in this issue) for allergic provocation of common migraine. The presumed association between epilepsy and migraine is tissue hypoxemia following intracerebral vasoconstriction. Is the different response, i.e., migraine vs epilepsy, simply a matter of rate of hypoxemia or extent or duration? If this is so, how can our present sequence of allergic mediator release explain intracerebral vasoconstriction? Egger et al.'s paper, though interesting clinically, is most difficult to explain.

Attention Deficit Syndrome

Shannon reported in 1922 that diet could affect learning ability and activity on a basis of sensitivity to foods *(51)*. For the attention deficit syndrome, also called hyperkinesis, hyperactivity, or "ants in the pants" disorder, a number of differing allergic problems have been suggested as causative. Sugar sensitivity, reactions to dyes and preservatives, other pharmacologic reactions of foods (caffeine), and immune-mediated food reactions have all been proposed and evaluated.

Table 1
Challenge Study of Sugar's Effect on Activity and Attention in Children

Authors	No. of subjects	Sugars tested[a]	Dose(s), g/kg	Placebo/ control[a]	Activity	Effect[b] of sugar on attention (CPT)
Behar et al.	21	S,G	1.75	X	–/=	=
Conners and Blouin	13	F,G	50[c]	OJ	+	
Conners et al.	37(13)[d]	S,F	1.25	A	–	(+)[d]
Ferguson et al.	8	S	1.5, 1.0, 0.5	A	=	=
Goldman et al.	8	S	2	A + L	+	–
Kruesi et al.	32	S,G	1.75	A,X	=	
Woolraich et al.	32	S	1.75	A	=	=

[a]The code for sugars and placebo/control is as follows: S, sucrose; G, glucose; F, fructose; L, lactose; X, saccharin; A, aspartame; OJ, orange juice.
[b]Symbols used: +, increased; =, no significant difference; –, decreased.
[c]Measured in grams.
[d]Subsample in parenthesis.
(As reported in Kruesi, M. J. P. and Rapoport, J. L. *[52].*)

Sugar (Sucrose) Sensitivity

There is a body of public opinion that considers sucrose an important cause of behavior problems in children. There are seven double-blind, placebo-controlled studies that measured sucrose's effects on behavior and attention. They are summarized in Table 1.

These studies provide evidence that even relatively large amounts of sucrose do not adversely affect behavior, except perhaps in some preschool children *(52).* The recent report of local cerebral dysfunction in glucose metabolism of adults who had been hyperactive is likely to raise the sucrose question again *(53).*

Dyes and Preservatives

Based on a few observations, Dr. Ben Feingold wrote a book for the lay community stating that dietary dyes, preservatives, and salicylates could cause attention deficit syndrome *(54).* This hypothesis was not subject to scientific study before being published. Testimonials as to the effectiveness of the diet manipulations abounded.

After this enthusiastic clinical response, and with some difficulty, placebo-controlled blind evaluations of the role, if any, for dyes and preservatives in hyperactivity were done. In no case was diet ever superior to adrenergic agents. In fact, only one subgroup of patients appeared to benefit from the diet. This again was the younger preschool child *(55).* Table 2 summarizes some of these studies.

Table 2
Trials of Feingold Hypothesis in Hyperactivity

Author(s)	Year	No. of subjects	Blinding	Results	Raters	Comments
Cook	1976	15	No	10 improved	P	Slight difference with order effect
Conners	1976	15	Yes	Diet better	P/T	Effect on younger preschool children
Harley	1978	36	Yes	Diet better	P/T	
		9	Yes	Blind challenges 1 of 9 worsened		
Goyotte	1978	16 diet responders	Yes	No effect of challenges		
		13 preschoolers	Yes	Challenges makes hyperactivity worse		
Williams	1978	26	Yes	8 better on diet	P/T	Effect of diet—modest Medication—more effect
Egger	1985	76	No/Yes	62 improved 21 normalized 28 improved subjects diet reintroduction leads to symptom recurrence	P/N/Psy	No effect on psychological tests in double-blind challenges

[a]P = parents; T = teachers; N = neurologist; Psy = psychologist.
(As reported in Feingold *[54]*.)

Reactions Presumably Involving Specific Antibodies or Sensitized Cells Causing Attention Deficit Disorder

Studies have looked at presumed immunological food reactions causing hyperactivity. Egger et al., using the same type of oligoantigenic diet mentioned previously noted improved behavior in 62 of 76 children studied. Many children appeared also to be adversely affected by benzoic acid and tartrazine. However, there were no children identified as solely reactive to one or the other or both of these agents. Forty-six different food sources provoked hyperactivity. During the oligoantigenic diet, 21 children's behavior normalized. During double-blind challenge diets, active foods were associated more often with behavioral changes than the placebos were *(56)*.

Kittler and Baldwin reported normalization of EEG abnormalities in 9 of 20 children with behavior disorders while they were on an elimination diet. No blinded challenges were performed. No performance changes occurred in tests of intellectual function, even when the EEG improved *(57)*. In one child with migraine and depressed intellectual performance, performance rose while he took oral cromolyn. It decreased when placebo was substituted for the cromolyn. The procedure was carried out in a blinded fashion *(58)*.

There are uncontrolled reports using neutralization provocation techniques to both stimulate and decrease hyperactivity. The recent blinded control study of this methodology, which demonstrated no difference between placebo and active substances, casts further doubt on the validity of the technique. This last study was important because it was performed by experienced practitioners of the technique *(59)*. There was not likely to be the investigator bias by opponents of the technique, which had flawed prior negative studies.

Pharmacologic Reactions

The final way in which diet may affect hyperactive behavior is a result of the pharmacologic excitatory activities of ingestants, such as caffeine in cola drinks or coffee, and phenylethylamine in chocolate. There seems to be marked intersubject variation in the catabolism of these agents. Insomnia and increased activity with a letdown and lethargic phase can occur. Large quantities of both aspartame and monosodium glutamate can be excitogenic in animal models. In large enough doses, they can also lower the seizure potential *(60)*.

Reviewing this area suggests that food or foodstuffs acting on an allergic basis are infrequent causes of attention deficit syndrome. The group most likely to benefit is preschool children. A large number of studies have tested the hypothesis that foods or food additives affect behavior and learning in children. There is substantial data

to conclude an effect of diet on affected children. In general, only those children with the milder behavioral changes benefit enough from diet changes alone to make this approach sufficient for their care. More severely affected children still require the other recognized means of treatment.

Tension–Fatigue Syndrome and Allergic Toxemia

In 1930, Rowe described a syndrome of allergic toxemia caused by food allergy *(61)*. The symptoms of this syndrome were drowsiness, mental confusion, lack of initiative, slowness of thought, fatigue, weakness, bodily aches, irritability, and a feeling of being poisoned. The patients often had gastrointestinal complaints. The average age of these patients was 45 yr. They were most often female. In many ways, these patients resemble subjects who today are described as having the chronic fatigue syndrome. Rowe reported great symptom relief with his modified diet approach. There were no double-blind challenges or controls in his studies.

In 1954, this symptom complex was renamed the "allergic tension–fatigue syndrome" by Speer *(62)*. He added the important concept of fatigue, which was not made better by rest, and stressed the occurrence of insomnia in some patients. He noted that the patients described an uncomfortable, nonphysiologic-sort of fatigue. He also reported that they had a total body achiness. He and others, such as Crook, believed that food allergy was an important provoker of this symptom *(63)*.

To date, only one controlled study of these patients regarding food-allergy provocation of the syndrome has been done *(63)*. This study is only partially accepted, if at all, by the general medical community. The described symptoms are common in patients visiting all types of physicians. It is extraordinary that a well-designed and controlled study has not yet been performed. In my clinical experience, which, includes only a few subjects who were challenged in a blinded fashion, the positive response to diet is difficult to explain. The single challenges were negative.

The first gut response is to call those patients who improved placebo responders. The difficulty with that approach is that it raises the question of why they did not respond to alternate therapies received before diet therapy. Two other important questions also must be addressed: First, what is the proper challenge for these patients? A longer exposure to the food or foodstuff may be required to simulate the natural situation. Second, there is the question of addressing in a measurable fashion the difference in the physiologic state of patients when they are feeling well as opposed to when they

are sick. To make this last concept clearer, an analogy to bronchial asthma, in which measurements are easier, can help. When an allergen bronchial challenge is performed, the bronchoconstrictive response is dependent on the degree of immunological sensitivity and the state of airway reactivity. Improving the physiologic state of the asthmatic and decreasing the state of airway reactivity will decrease the bronchoconstrictive response, without change in the specific sensitivity to the allergen.

In the lung, the state of airway reactivity can be measured and inferred from methacholine, histamine, or other challenge studies. Because of this, the changes described earlier no longer seem mysterious. I am unaware that such a measure of reactivity has been described and evaluated for patients with complaints such as those found in the tension–fatigue syndrome. Lacking this, we will have tremendous difficulty in scientific evaluation of these patients.

Therefore, discussions and honest differences of opinions based on observations and personal interpretations will remain until this last issue can be resolved. Challenging prior to therapeutic response is one solution, but rarely done. A second method may involve monitoring the state of basophils or platelets in the peripheral blood as indicators of nonspecific reactivity. In our present climate, I am not optimistic that a study of these concepts related to tension–fatigue syndrome would be funded.

Ménière's Syndrome, Vertigo, and Fluctuating Hearing Loss

Duke described five patients with Ménière's syndrome who experienced relief when given epinephrine injections. They were then placed on elimination diets with long-term relief *(64)*.

The notion of food allergies causing hearing problems and/or vertigo along with the more classic Ménière's syndrome is a common idea among otolaryngologic allergists *(65)*.

There are no well-done double-blind controlled studies. Unfortunately, most recent studies addressed the provocation and then neutralization of these symptoms. As mentioned above, other mechanisms, especially a strong suggestive component, are likely to be operant with this technique.

There is a disorder described in infants and young children called benign paroxysmal vertigo with fluctuating hearing loss. Affected patients improved on an avoidance diet. Challenges with milk provoked the symptoms. This is perhaps the best information concerning food-induced effects on the vestibular and auditory organs *(66)*.

Paralytic Syndromes

Transient hemiplegia with associated allergic symptoms following open ingestion of certain foods was reported by Stafferi in 1952 *(67)*. According to the authors, other similar cases had been described.

Insomnia

Kahn reported the benefit of cow-milk avoidance in infants who were fitful sleepers or insomniacs. The children were observed in a pediatric sleep laboratory. Removing cow-milk formula improved the quality and quantity of sleep. Reintroduction of cow milk apparently caused return of insomnia. Specific anti-cow-milk Ige antibodies were not demonstrable *(68)*.

Multiple Sclerosis

Patients with multiple sclerosis have increased frequency of allergic disorders compared to the general population *(69)*. Stimulated by this observation, studies to prove a role for food allergies in causing multiple sclerosis were done. They were not able to demonstrate a connection *(70)*. At this time, there is no basis to consider food allergy to cause multiple sclerosis, as it is presently defined.

Psychiatric Disease

This is a most difficult area to define. Our understanding of psychiatric disease is constantly changing. There are a great deal of "chicken and egg" questions. Does thought produce the metabolic product? Does the mediator produce the thought? Does food-induced mediator release affect the brain? It is clear that the allergic mediators are active in the CNS.

A few case reports concerning food-induced psychiatric disorders have been reported, the best of which involved food-induced depression in a nurse. Diet manipulations were initially based on clinical observations with relief of symptoms. Blind challenges were done to confirm the relationship *(71)*.

An idea once very popular was that food could cause "nervous storms." In these cases, a generally rational person would have outbursts of irrational behavior without apparent reason. The concept was firmly held by a group of eminent physicians, including Dr. Walter Alvarez, a prolific writer and editor of medical literature *(72)*. This area has not been addressed other than in clinical reports.

Dohan noted that the incidence of reported schizophrenia decreased in the occupied countries of Europe during World War II *(72)*. The amount of wheat in the people's diet was less, as the Nazi

occupiers appropriated it for their troops. He speculated that gliadin sensitivity might cause or worsen schizophrenia. Based on this gliadin concept, schizophrenics and patients with other psychiatric disorders were placed on a wheat-free diet. Dohan reported a more rapid rate of improvement in patients on the wheat-free diet than in those taking the usual diet containing wheat *(73)*. Subsequent studies have both confirmed and refuted these results *(74,75)*.

Left-Handedness and Allergic Disease

Perhaps no other experiment of nature provides so many examples of how the brain can affect the allergic response. There is a statistically important increase in the frequency of allergic disorders among the left-handed population compared to right-handers *(76)*. Left-handedness is associated with an increased propensity to autoimmune disorders *(77)*. There appear to be important cerebral controls of the immune response. Alternatively, genes that code for disorders of immunoregulation may be closely linked to the genes that determine altered cerebral dominance.

Candida *Sensitivity or the Yeast Connection*

The ability to rationally discuss the concept that *Candida albicans* species causes a variety of patient symptoms appears to have disappeared because of hyperbole and abuse by its proponents. An incredible number of in vitro and in vivo clinical observations have been bundled together to force a relationship. There are valid questions and ideas put forth by the advocates of the syndrome. However, they are not kind enough to apply stringent and consistent methodologies to prove their points. Additions and folklorelike myths abound in the clinical practices and descriptions of "Candidiasis." These practices disturb a balanced view by providing poor information to evaluate.

The story of Candidiasis is not over. If there is any value in it, then time will sort it out after the passionate opinions wane. The idea that the alterations in our diets and our use of antibiotics and corticosteroids can have other than the presently accepted effects is not fatuous. The spectrum and range of disorders attributed to changes in one body ecosystem from this use appears to involve perseveration.

Summary and Clinical Advice

Clinical beliefs and observations of allergic disease mechanisms of nervous system disorders appear to be partially valid. The claims suffer from exaggeration and inadequate proofs. It is important to

have these controversial ideas studied in well-controlled scientific investigations, with adequate numbers of subjects. If we suppose that a subset of people manifest allergy-induced neurologic or psychologic disturbance, then the evaluation is worthwhile. In general, reasonable dietary modification with attention to nutritional values is superior to pharmacologic interventions.

Given the imperfect information in this area, each individual physician must decide for himself or herself on an approach to these patients. This is not as difficult as it sounds on first blush.

Honesty and *primum non nocere* are good guides. When a patient asks about allergic reasons for unusual symptoms, based perhaps on a TV show or magazine article, we discuss the present facts as they exist. We make certain that, as much as possible, other causes for the complaints have been evaluated. In most cases, this is already true by the time he or she visits our office.

Explanation, stringent observation, and objective measurements when possible are the key to exploring such areas with patients. If dietary modification is planned, a baseline symptom-monitoring period on the usual diet is very useful. If during the modified diet the patient improves, reintroduction with continued monitoring is done. During this phase, suspect allergens may be identified. The patient, if agreeable, is then given blinded challenge to the suspected items. Informed consent and understanding along the entire process must be documented.

Patients are almost never advised to restrict their diets unless they demonstrate responses on the blind challenges. However, some patients choose to avoid certain foods based on their own beliefs and observations, without physician advice. In these cases, I attempt to ascertain that the avoidance is not likely to harm them and will provide adequate nutrition. Until more information is available, this approach seems the most suitable for "real world" allergy practice.

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