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Food Allergy — Cytotoxic Testing and the Central Nervous System†

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The term allergy most commonly refers to skin and respiratory reactions to contact and inhalant allergens. Of increasingly more recognized importance, however, are allergic responses to specific foods. Such food allergens are in intimate contact with every segment of the gastro-intestinal tract, are taken into the blood stream and reach the micro-circulation of every organ in the body. Thus food allergy can produce a variety of symptoms, can imitate many diseases and, as well, exacerbate other existing allergies.

The author is particularly interested in allergies of the central nervous system and he reviews important literature of the past few decades which tabulates the symptoms of cerebral allergy ranging from simple dizziness and syncope to seizures, depression and anxiety attacks.

The problem of identifying the offending foods is often difficult. Skin testing is very unreliable while elimination diets are cumbersome and difficult for the patient. Confrontation tests may be confusing to interpret and can produce untoward reactions.

The author has found the Cytotoxic Test satisfactory for both research and clinical work. It requires only a single fasting blood sample and permits the direct interpretation of neutrophile reaction with any number of test food extracts.

Foods so identified, when ingested, have been shown to produce both clinical symptoms as well as transient leucocytosis. In blind testing, such reactions did not occur with neutral foods. Dose response curves have been developed. A similar reaction to tobacco smoke in the air was found.

Testing for food allergy is a useful addition to psychosomatic practice.

To most physicians, the term allergy is reserved only for reactions to substances that touch the skin (contactant eczema, urticaria, etc.) or that are inhaled into the respiratory tract (dust and molds causing asthma and hay fever, bronchitis, etc.). The average U.S. physician is not inclined to look to food substances as agents likely to cause symptoms within the cardio-respiratory, musculo-skeletal, genito-urinary, endocrine or central nervous system. Thus patients with vague complaints and seemingly undiagnosable illness may in fact be suffering from food allergy. When food allergy goes unrecognized as a cause of such symptoms, these patients may be referred to a psychiatrist as having 'nervous' or 'psychiatric' disorders.

Although historically reactions from sensitivity to foods have been recognized since the time of Hippocrates, it has been only in the last half century that food allergy has been discussed in the medical literature.[17]

The basic pathogenesis of allergic lesions occurs when allergen and antibody combine with or without complement or other adjuvants to produce local cellular edema and cell breakdown with the release of histamine, kinens, prostaglandins, serotonin, S.R.S., catecholamines, etc., with resultant swelling, redness, itching and pain. Such lesions can occur not only with the allergen contacting the skin or respiratory mucus membrane, but anywhere within the body where allergens may reach the local micro-circulation. It is particularly significant for the psychiatrist to recognize that this type of reaction in brain tissue may be responsible for emotional and behavioral symptoms.[1,9,10,16,24]

Table I lists those diseases that have been recognized as caused or aggravated by allergic reactions. It is not coincidental that this list contains many illnesses commonly labeled as 'psychosomatic', for it has long been recognized that emotional problems can aggravate allergic illness and *vice versa*. When a person is in good emotional control, allergies are less likely to be troublesome.

The recent discovery of a center in the ventral hypothalamus that controls anaphylaxis in the guinea pig seems to establish a neuroanatomical basis that is common to allergy and emotions. The role of endorphins in the production of releasing factors from the

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hypothalamus is further evidence linking the central nervous system and endocrine glands in a manner that can affect both emotions and allergy.

The direct effect of food allergy on the central nervous system is well-documented. In his milestone publication, *Nervousness, Indigestion and Pain*[1] Walter Alvarez described his own experiences with what he termed, "dumb Mondays", characterized by sluggishness, ennui and difficulty in thinking occasioned by eating chicken habitually on Sundays. More recent books on this subject have supplied lengthy bibliographies in support of this thesis.[9,10,16,24] These books document the extensive clinical experience showing that ingested foods can, in susceptible persons, induce a wide variety of neurological and psychiatric symptoms.

As early as 1700 reports appeared in the literature of convulsive seizures occurring after ingestion of specific common food substances.[5] In 1916 Hoobler,[9] described a child with irritability, fitfulness and insomnia following ingestion of an allergenic food.

In 1930 Rowe[14] and Vaughn[23] introduced the term 'auto-intoxication' and pointed out that fatigue and weakness were common symptoms of food allergy and in 1954 Speer[18] introduced the term 'allergic tension fatigue syndrome' so commonly seen in hyperactive and M.B.D. children. In 1952 Davidson[7] enumerated the nervous and mental disorders that had been found associated with food allergy (Table II).

The mechanism of such a wide variety of symptoms may be traced to the action of allergen upon focal areas of brain tissue. As the work of Wilder Penfield clearly demonstrated, focal stimulation of brain tissue can produce specific and repeatedly demonstrable effects.[11] The patho-physiology of allergens carried by the microcirculation of the brain to specific sensitized areas could well account for any or all of the above listed symptoms. Target organs of central nervous system allergy can include cortex, thalamus, limbic system, brain stem or hypothalamus with the latter responsible for widespread autonomic or endocrine disturbances. Chronic exposure to food allergens could thus produce continuing changes in catecholamines with behavioral alterations that do not quickly reverse.

Food allergy can be quite specific to a single food or to a family of foods. Often allergy to a specific food seems to be inherited. We have tested the cord blood of newborn babies before any food entered the gastrointestinal tract and found by Cytotoxic Food Testing, a sensitivity to foods to which one or both parents were allergic.

In some instances, there seems to be only the allergic tendency which is inherited and allergy to specific foods is then acquired through exposure. In this way, any food may be a potential allergen.

In some cases, as with angioneurotic edema, the reaction to a food may be instantaneous. More often it is delayed for 30 minutes to eight or ten hours. A longer time may indicate a sensitivity to some breakdown product of metabolism rather than to the whole food itself. Food allergy may be additive and with foods remaining in the body for several days, reactions can be delayed by that length of time.

The amount and frequency of feeding is important and we have demonstrated typical dose response cur-

TABLE I
DISEASES CAUSED OR AGGRAVATED BY ALLERGIC REACTIONS

Respiratory System:	Hay fever with rhinitis and conjunctivitis, bronchitis with symptoms from tobacco and petrochemicals, asthma and sensitivity to inhalants, foods and chemical and in all of these, an increased sensitivity to respiratory infections — all aggravated by food sensitivities.
Skin:	Angio-neurotic edema, urticaria (hives), pruritis (itching), eczema — again primarily from ingested food or contactant allergen worsened by food allergy.
Digestive System:	Apthous ulcers (canker sores), dyspepsia (indigestion), peptic ulcer, regional ileitis, Crohn's disease, constipation, diarrhea, colitis and rectal irritations.
Cardio-Vascular System:	Dysrhythmias, vaso-vagal attacks (syncope, fainting, giddiness), anginal pain, hypertension.
Musculo-Skeletal System:	Arthralgias, arthritis and myositis.
Genito-Urinary System:	Frequency, impotence and frigidity.
Endocrine System:	Hypothyroidism, hyperthyroidism and dysmenorrhea.
Central Nervous System:	Headache (including migraine), convulsions, tinnitus, vertigo, anxiety, hyper-irritability, hyperactivity, depression, lethargy, lack of energy, insomnia, inability to think clearly, thought disorders.

TABLE II
NERVOUS AND MENTAL DISORDERS ASSOCIATED WITH FOOD ALLERGY[7].
(Davison, 1952)

Emotional Immaturity	Syncope
Antisocial Behavior	Vertigo
Depression	Ataxia
Anxiety	Tinnitus
Organic Brain Syndrome	Myoclonus
Temporary Deafness	Numbness
Nerve Palsies	Impotence
Neuralgias	Diplopia
Urinary Incontinence	Blurred Vision
Hemiplegia	Micropsia
Convulsions	Macropsia

ves in response to eating steadily increasing amounts of a food to which a subject was allergic. Temperature changes (chilling), an allergic 'loading' effect of other allergens (respiratory, contactant, etc.) has been noted as well as the effect of infections in increasing the sensitivity to allergens.

The concept of 'masked' food allergy introduced by Rinkel[13] has been expanded by Randolph[12] to explain chronic alcoholism and addiction to caffeine, tobacco and drugs. Mackarness[9] explains masked food allergy in terms of Selye's[15] three stages of general adaptation. In stage one, food to which one is sensitive is eaten only occasionally, producing some occasional ill after-effects. In stage two, the food is regularly ingested, stimulating body resistance or 'adaptation' with a feeling of 'pick-up' after a meal in which the food is eaten. Finally, more frequent and larger doses are needed to produce the same level of alertness — passing on to more frequent hangovers until finally, in stage three, the adaptive mechanisms are exhausted and symptoms occur with increasing frequency and severity.

Food allergy is suspected when the patient complains of persistent fatigue, puffiness of the face, hands, abdomen or ankles, palpitations (particularly after food), excessive sweating unrelated to exercise, over or underweight and a fluctuation of these and other bizarre symptoms, including emotional and behavioral dysfunction. Digestive disturbances and headache are very common. Often the patient speaks of an intolerance or 'opposite reaction' to various medications.

The patient with food allergy may well exhibit the telltale signs of allergy: dark circles under the eyes, stuffy nose causing nasal speech and mouth breathing, watery eyes and a white coated tongue.

Our own research into food allergy began with a look at food allergy in alcoholics.[19] We were intrigued by the many alcoholics who told us that they were 'allergic' to alcohol.

Initially we puzzled over how best to detect such an allergy. We knew that skin testing was notoriously unreliable (reportedly only about 25% accurate). Elimination diets are cumbersome and difficult for the patient to follow, while confrontation tests are not always easy to interpret and at times produce severe reactions.

We then learned of the cytotoxic food test from St. Louis colleagues, William and Marian Bryan.[4] For this test, 10 cc. of blood is taken from the

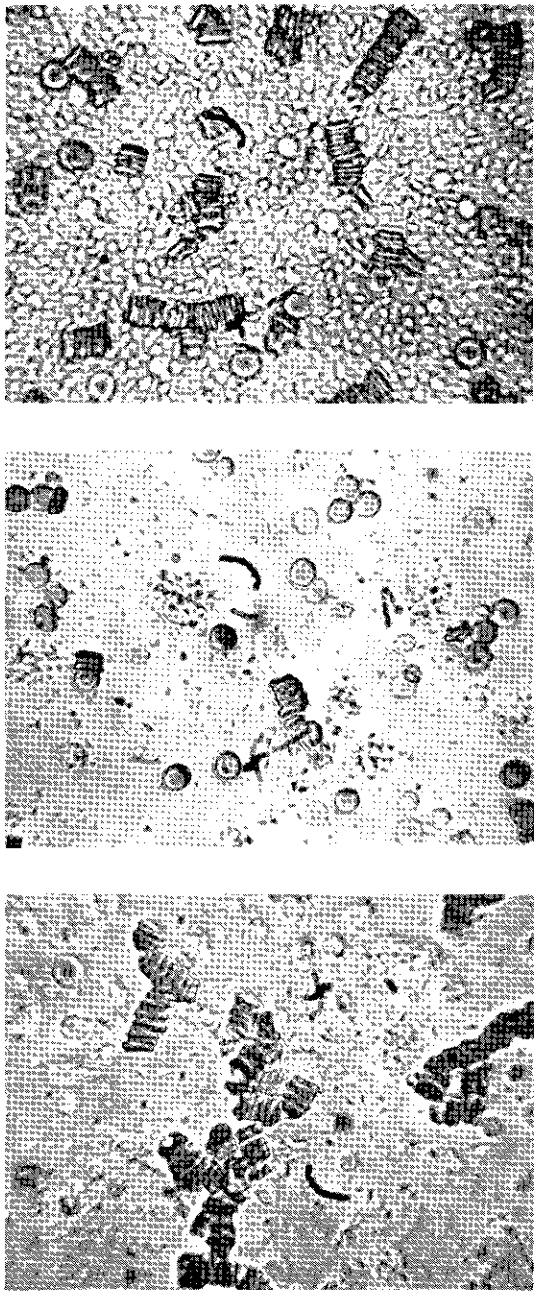

FIGURE 1
Photo-micrographs of unstained buffy coat slide preparations. 1 shows control slide. 2 and 3 show cytotoxic reactions of blood cells in contact with food antigens.

patient who has been fasting 6-8 hours. This blood sample is centrifuged and the buffy coat drawn off, diluted and mixed with separate samples of food allergens. The white cell/allergen mixture is observed under the microscope after two hours. The test is read by a trained technician who grades the amount of toxic reaction in each preparation and reports it as 0 to 4 plus. (Figure 1)

The dependency upon the technician's subjective readings is the weakest part of the test, although we have obtained fair retest reliability on between-rater readings. Unlike other ways of detecting food allergies, the cytotoxic test is easy on the patient, quickly repeated and adaptable to research methodology. Our own experience and that of other physicians have found this test to be clinically valid and useful. [2,22]

In our first research procedure, we compared the amount of food allergy as determined by cytotoxic testing of 70 foods in 25 male alcoholics, 25 volunteer controls and 25 Alcoholics Annonymous members who had been abstinent for a minimum of six months. Mean ages were 49, 36 and 45 years respectively. Alcoholics were seen within three to fourteen days of hospital admission.

Figure 2 shows that the alcoholics had roughly twice the amount of food allergy seen in either the control or A. A. sample. The results were all significant.* The greatest sensitivities for the alco-

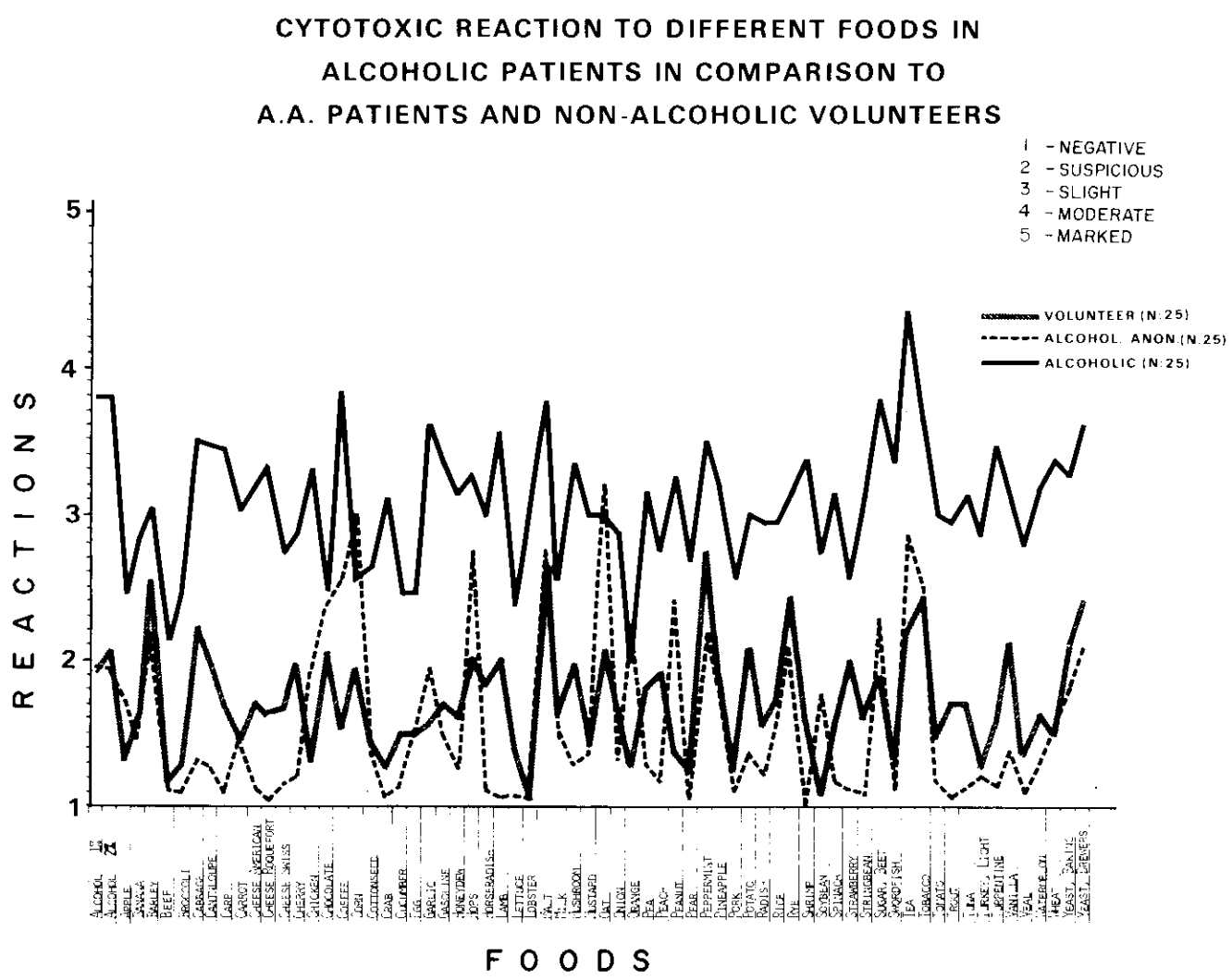

FIGURE 2

Group Profiles of Cytotoxic Reaction to 69 Food and Other Antigens in 25 Alcoholic Patients, 25 Nonalcoholics and 25 A. A. Members. The cytotoxic reactions were rated on a scale of 1 to 5: 1 = negative, 2 = suspicious, 3 = slight, 4 = moderate and 5 = marked reactions.

* Between alcoholic and control < .0005, between alcoholics and A. A. < .005 and between non-alcoholic controls and A. A. < .05.

holics were tea, alcohol, coffee, beet sugar, malt and tobacco.

Because there was a significant difference between the drinking alcoholics and the non-drinking alcoholics (A. A. group), it was clear the higher food sensitivity was not something characteristic of persons who become alcoholics, but rather, was related in some way to the recent use of alcohol. This seemed further evidenced by the fact that the control group, containing social drinkers, had more allergy than the A. A. group who did not drink at all.

The major conclusion to be drawn from this study is that when a person drinks he enhances his food allergies. In support of this is work by Davenport[6] who found that in dogs, alcohol, aspirin and bile salts all damaged the gut lining, permitting the passage of larger food molecules. Also, chronic alcoholics are metabolically ill persons and this too may have contributed to the greater amount of food allergy in the patient sample.

From our own clinical experience and that of William Bryan on more than 6,000 patients,[3] we were convinced of the practical clinical validity of this test. We however felt that it would be useful to find a method to determine validity independent of clinical opinion. Studies in our laboratory[20,21] involved first, the testing of ten subjects on our battery of 70 foods, with findings of an average cytotoxic sensitivity to 24% of the food antigens used. On separate days and in random fashion we first gave each subject a meal consisting of foods to which he was found sensitive and then a meal of foods to which he was not sensitive. By means of finger-stick collection, blood samples were drawn before the test meal and every 30 minutes thereafter for three hours. As can be seen from Figure 3, *in vivo* leukocytosis was obtained following the consumption of foods to which the subject was sensitive. No such rise in total WBC count was found following the consumption of non-allergenic foods. Differential cell counts were unchanged. All WBC counts returned to baseline within three hours.

Cytotoxic tests run during exposure to sensitizing foods often increased the degree of reaction to other foods that were negative or low on initial testing.

Dose response curves were also examined on several subjects and showed an increasing response to the consumption on subsequent days of increasing amounts of chicken, chocolate and peanuts, all of which were sensitizing foods for the tested subject.

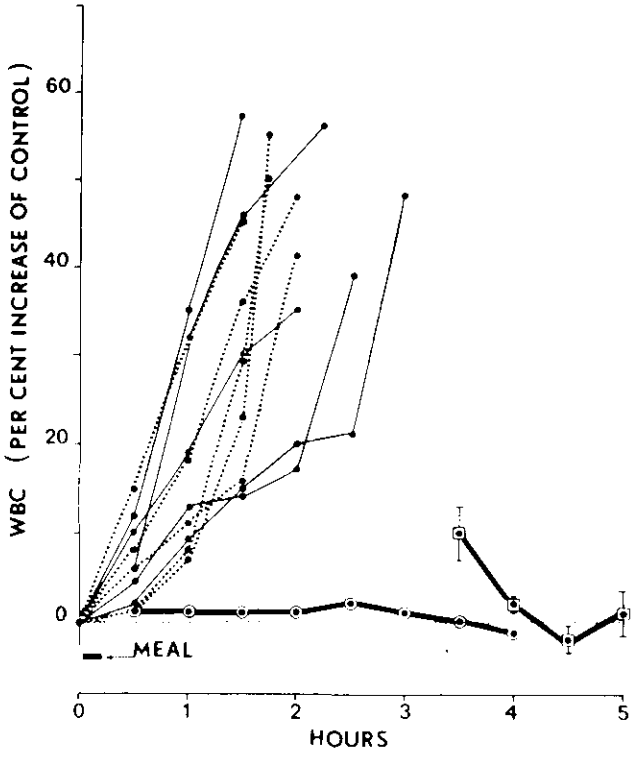

FIGURE 3

Sensitizing food-induced peripheral white blood cell (WBC) increase in five male (solid lines) and five female (hatched lines) prefasted subjects, with the return to control values (open squares) plotted as an average for the group ± S.E.M. Nonsensitizing food tested controls (open circles) were run on the same subjects on the morning following their allergenic test.

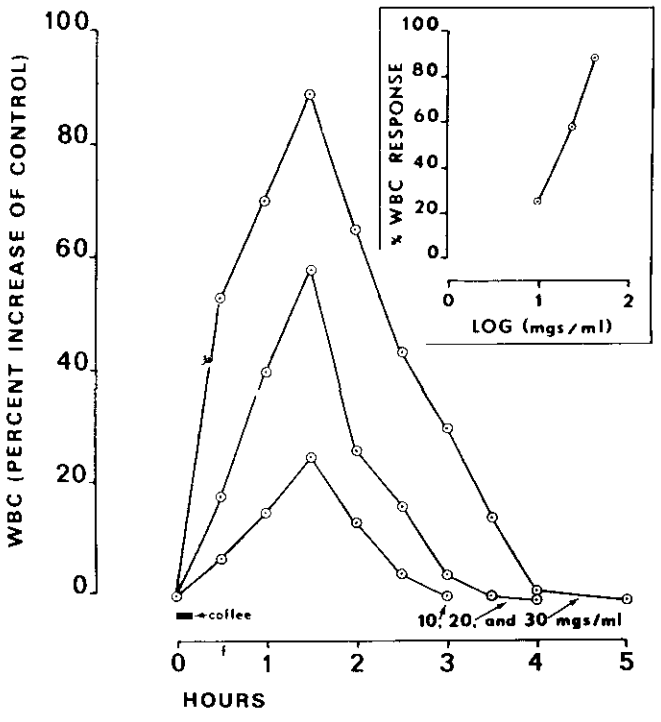

FIGURE 4

Peripheral WBC responses to coffee. *In vivo* WBC response test with dose-response data indicating magnitude and time course of the WBC response, also expressed as a dose-response curve (Figure inset), following a ten minute period during which a measured amount of coffee was consumed.

As seen in Figure 4, coffee-sensitive subjects who drank two cups of dried frozen coffee showed prompt increases in total WBC count as a result of exposure to their antigens. Increasing amounts of coffee increased the WBC respectively in typical dose-response fashion (Figure 4). In tobacco-sensitive subjects who smoked two king size filter cigarettes, an increase in WBC cell count occurred. Subjects who were not sensitive to tobacco but similarly exposed showed no such response (Figure 5).

It is of interest that the *in vitro* tobacco test involved contact between the WBC cells and tobacco extract while the *in vivo* reaction involved contact with the volatile ash. A further experiment demonstrating the antigenic power of such volatile substance involved placing non-smoking tobacco-sensitive persons in the same small room with two smokers. The latter smoked two king sized filter cigarettes. The air pollution from their cigarettes was sufficient to induce a WBC increase in the non-smokers.

From clinical work with the cytotoxic test, we have become increasingly impressed by the wide variety of symptoms that appear to be linked to food sensitivity. Severe depression with suicidal attempt, migraine-type headaches with nausea and vomiting, hyperactivity and impulsive behavior, retro-orbital pain, lack of energy, weakness and anorexia, migratory arthritis and sleep disturbances — these are but a few of the myriad symptoms seen in our patients who have been found by cytotoxic testing to have specific food allergy. Such patients as these have improved markedly on diets eliminating those foods

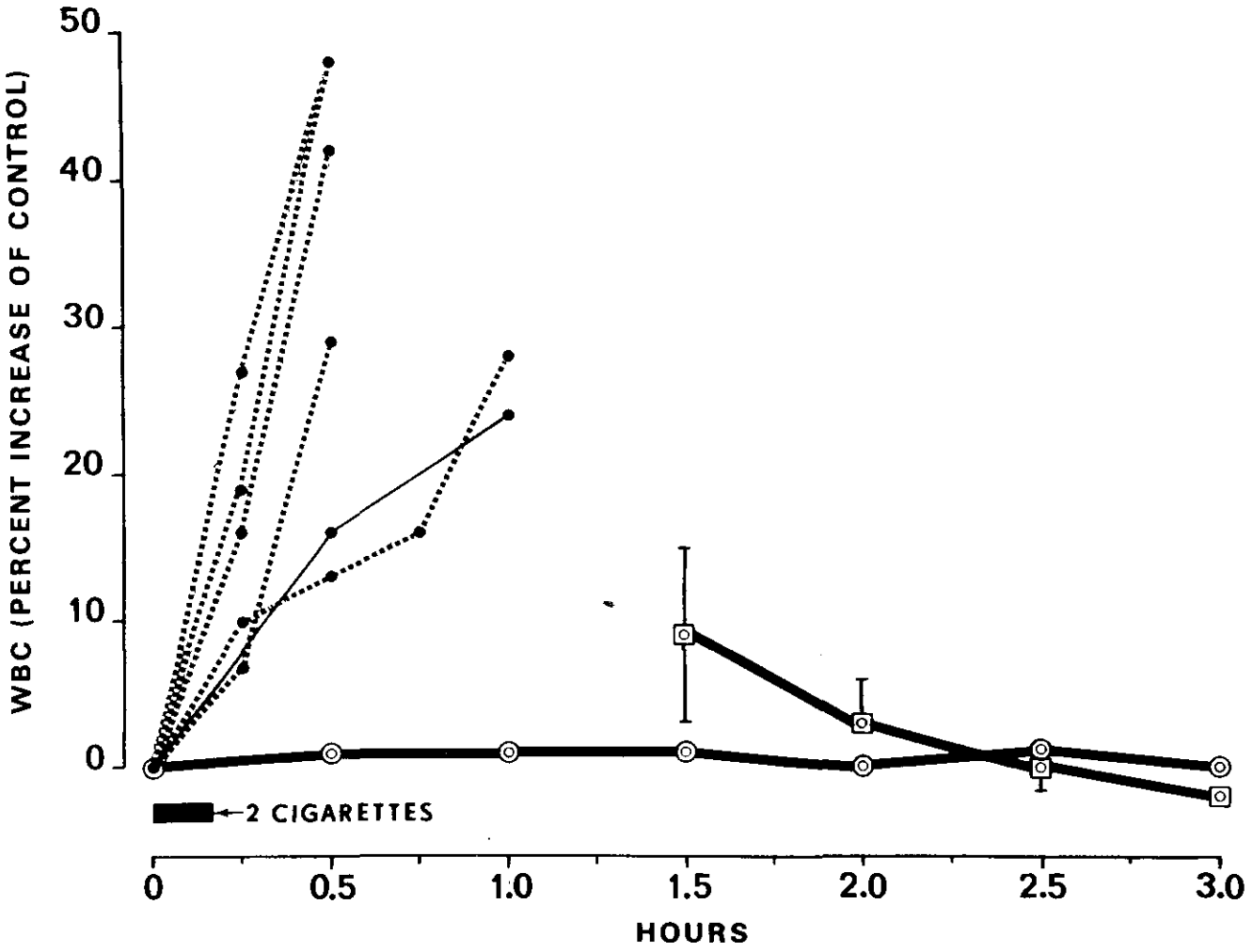

FIGURE 5

Peripheral white blood cell (WBC increase in five female (hatched lines) and one male (solid line) prefasted subjects) in response to smojing two filter king cigarettes within ten minutes. The return to control values (open squares) was plotted as an average for the six subjects ± S.E.M. Three prefasted regular smokers determined tobacco insensitive by the Cytotoxic Test procedures failed to show a peripheral WBC response (open circles).

to which they reacted positively. Our clinical experience mirrors that of other physicians who have reported in the literature.[2,3,22]

Most recently our research efforts have included attempts to monitor other physiological indicators of food sensitivity. In this we have followed our original design of feeding subjects antigenic and non-antigenic foods as determined by cytotoxic food testing. In order to maximize the effects we use 2-3 foods, eaten after a 6-8 hour fast. Figure 6 shows a rise in pulse rate which typically accompanies the rise in WBC count. Figure 7 shows a desynchronization of the EEG that accompanied the WBC and pulse elevation in one subject whose symptoms included gastrointestinal disturbances, fatigue and headaches.

The treatment of food allergies consists initially in following the diet from which the offending foods are carefully omitted. We recommend that patients remain on such diets indefinitely and indeed, because of the symptom relief experienced, most patients are willing to do this. When the diet has been free of a given allergenic food for a week or more the reintroduction of this food may cause a sudden and severe reapperance of the patient's symptoms which again abate when the diet is reintroduced. Should the food be a common one, difficult to avoid, it may be cautiously reintroduced after three to six months but even then eaten no oftener than once a week. As the sensitivity to some allergies will subside while new sensitivities develop, we recommend re-testing our patients every one to two years.

Whereas an avoidance diet is the surest and best way to avoid symptoms, some physicians attempt specific food desensitization. This is usually accomplished by using a weak solution of the antigenic food, beginning by placing one drop sublingually t.i.d. and increasing each day until a reasonable amount of the food is tolerated. Even then, the food should be eaten sparingly and no oftener than once every five to seven days.

CONCLUSION:

Today there is increasing evidence that food allergy plays a major role in producing somatic and

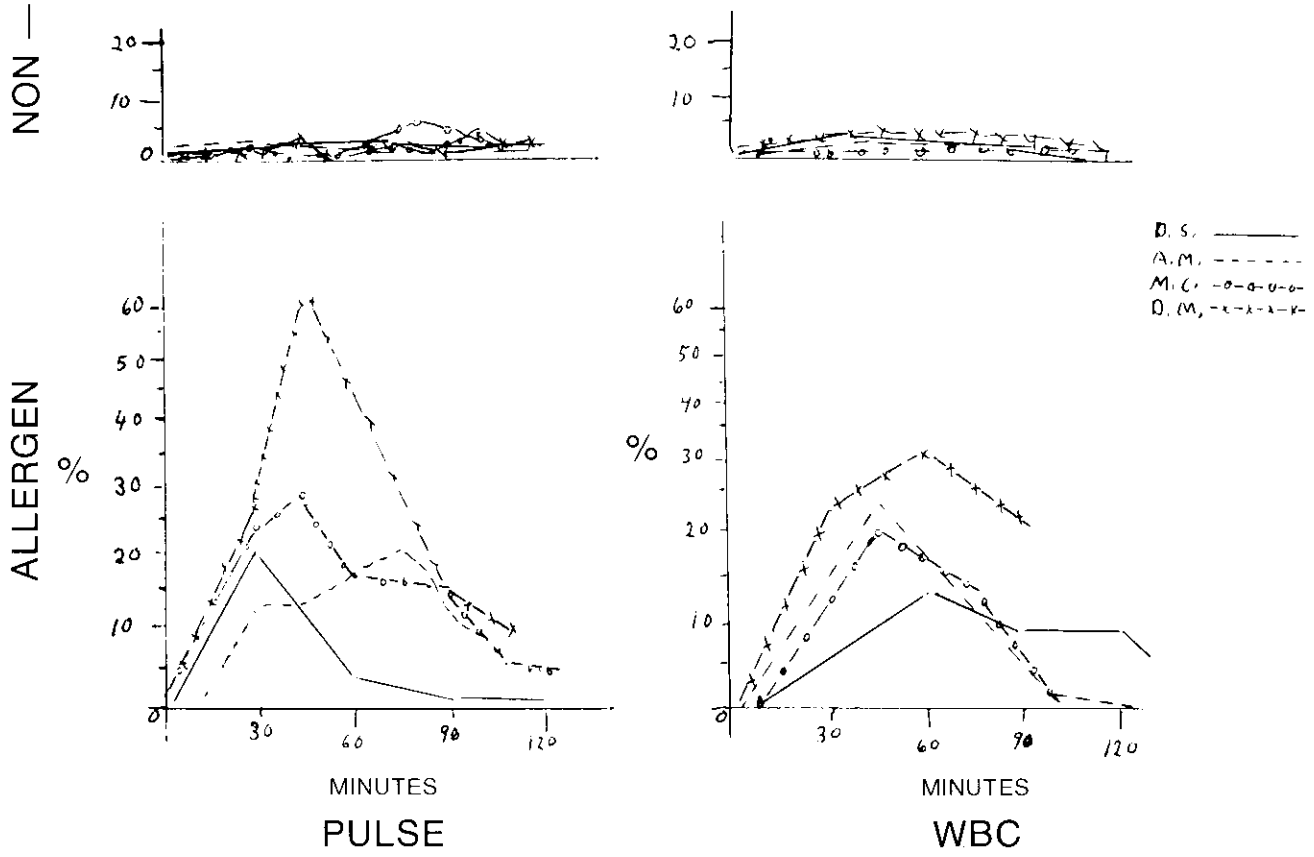

FIGURE 6

Graphs showing correspondence of increases in pulse rate and WBC count in four individuals following the ingestion of food allergens. No such increases were seen with food to which they were shown not sensitive by Cytotoxic Testing.

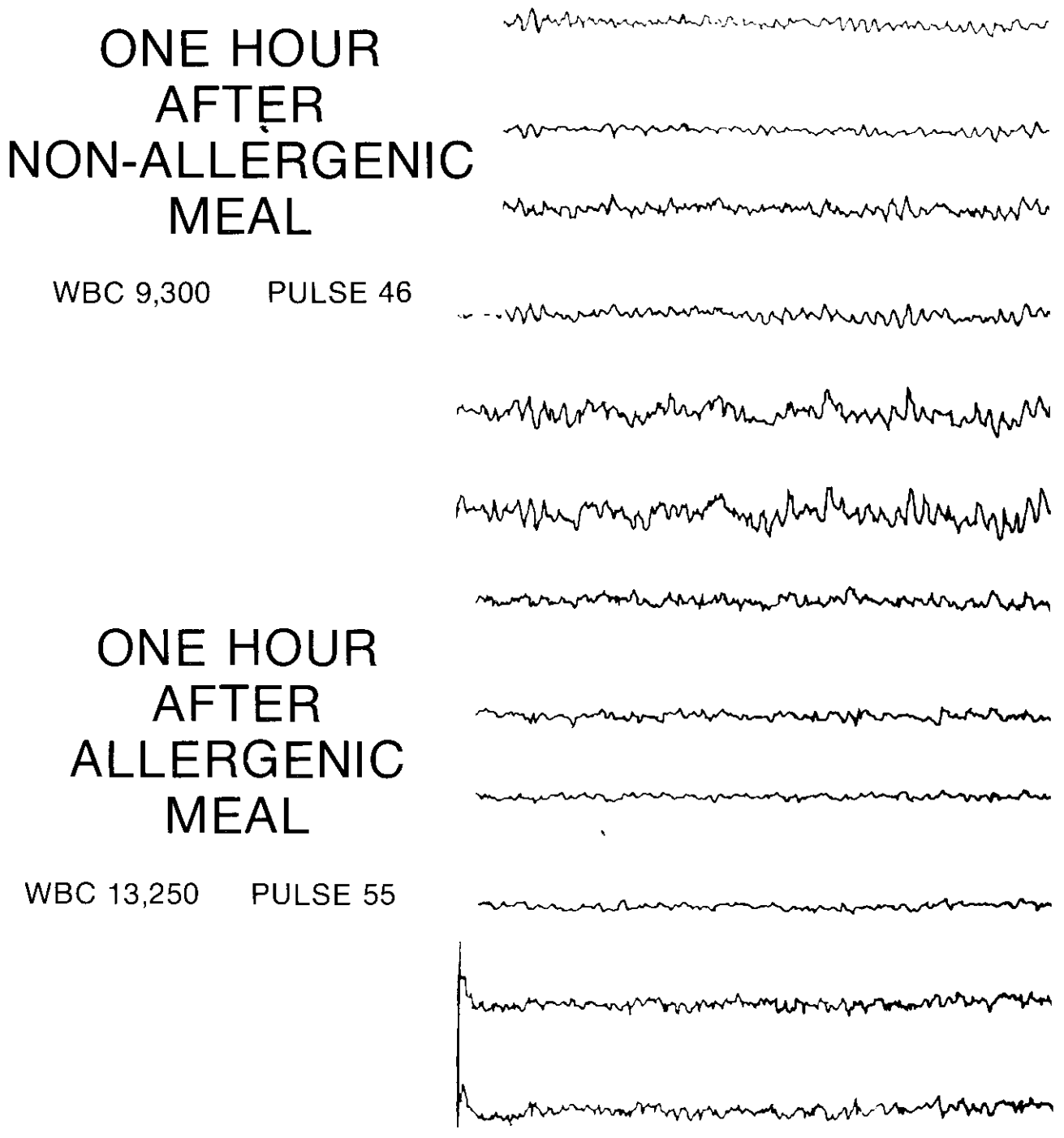

FIGURE 7
Desynchronization of the EEG seen after the ingestion of allergenic foods. Note increase in WBC count and in pulse rate which accompanied the EEG alteration.

behavioral symptoms that have in the past been commonly labeled as 'neurotic' or 'psychosomatic'. It is thus important for the psychiatrist to think of the possibility of cerebral allergy in patients whose symptoms are atypical and fail to respond to traditional treatments. We believe the cytotoxic test for individual food sensitivity is a useful tool which has promise both for research and for the clinical control of food allergy.

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