Clinical Evaluation of the Major Plasma and Cellular Measures of Immunity

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Abstract

After demonstration by Rea et al. of cellular and humoral alterations in food and chemical reactions, McGovern and others initiated a long term study of the immune status of patients in whom food and chemical sensitivities had been observed. Their findings suggest that immunologic abnormalities play an important and, perhaps, central role in their symptomatology.

Their study included testing of several aspects of immunologic function. These areas include complement parameters (CH-100, C-3 and C-4); immunoglobulins (IgA, IgG, IgM, IgD, IgE and immune complexes of the IgG type); chemical mediators (serotonin, histamine and prostaglandins F2a); and cellular immune assays (T and B cells and the T cell subsets: helper and suppressor cells).

The authors describe several patterns which correlate with the presenting complaints. They conclude that study of immunologic parameters is of importance to physicians *treating patients presenting with a range of symptoms including CNS, respiratory and gastrointestinal systems.*

The authors provide laboratory guidelines for the practicing physician. They outline a testing strategy aimed at documenting the organicity of symptom complexes in patients presenting to physicians specializing in clinical ecology, Orthomolecular psychiatry and related fields.

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Introduction

Rea et al. (1978) demonstrated that both humoral and cellular alterations are at the basis of food and chemical reactions. Subsequently, in 1979, Drs. McGovern and Lazaroni initiated a long term study of the immune status of patients suffering from food and chemical sensitivities which appear to be induced by environmental factors. The clinical characteristics of the patient population we studied are recorded in Figure 1 where it can be seen that phenol sensitivity was present in every case.

After studying approximately 125 patients with food and chemical sensitivity, we found a particular group of humoral immune abnormalities present (Fig. 2). In collaboration with Drs. Saifer and Levin, we also

found significant depression in T cells in these patients (Fig. 3). We found individuals with primarily inhalant or pollen sensitivity show a quite different complex of abnormalities in their plasma, e.g. elevated histamine and IgE levels.

Later, in collaboration with Doris Rapp, M.D. of Buffalo, New York, we have also studied the effect of oral, inhalational and intradermal challenge with specific food antigens on the plasma and cellular immune components. As a result of these studies, we now recognize a pattern of serial plasma alterations consistent with one or more of the classical immune responses described by Gell and Coombs. Dr. Rapp was first to observe some previously unreported biochemical abnormalities in some patients after challenge. For example, she found marked changes in erythrocyte sedimenta--tion rate and in specific IgE levels following intradermal provocative challenge. Since then we have expanded our studies to include evaluation of neuropeptide hormone response to provocative challenge (Table 1). The discussion which follows provides the clinician with an updated discussion of the principles and practice of laboratory testing for the physician treating ecologically ill patients.

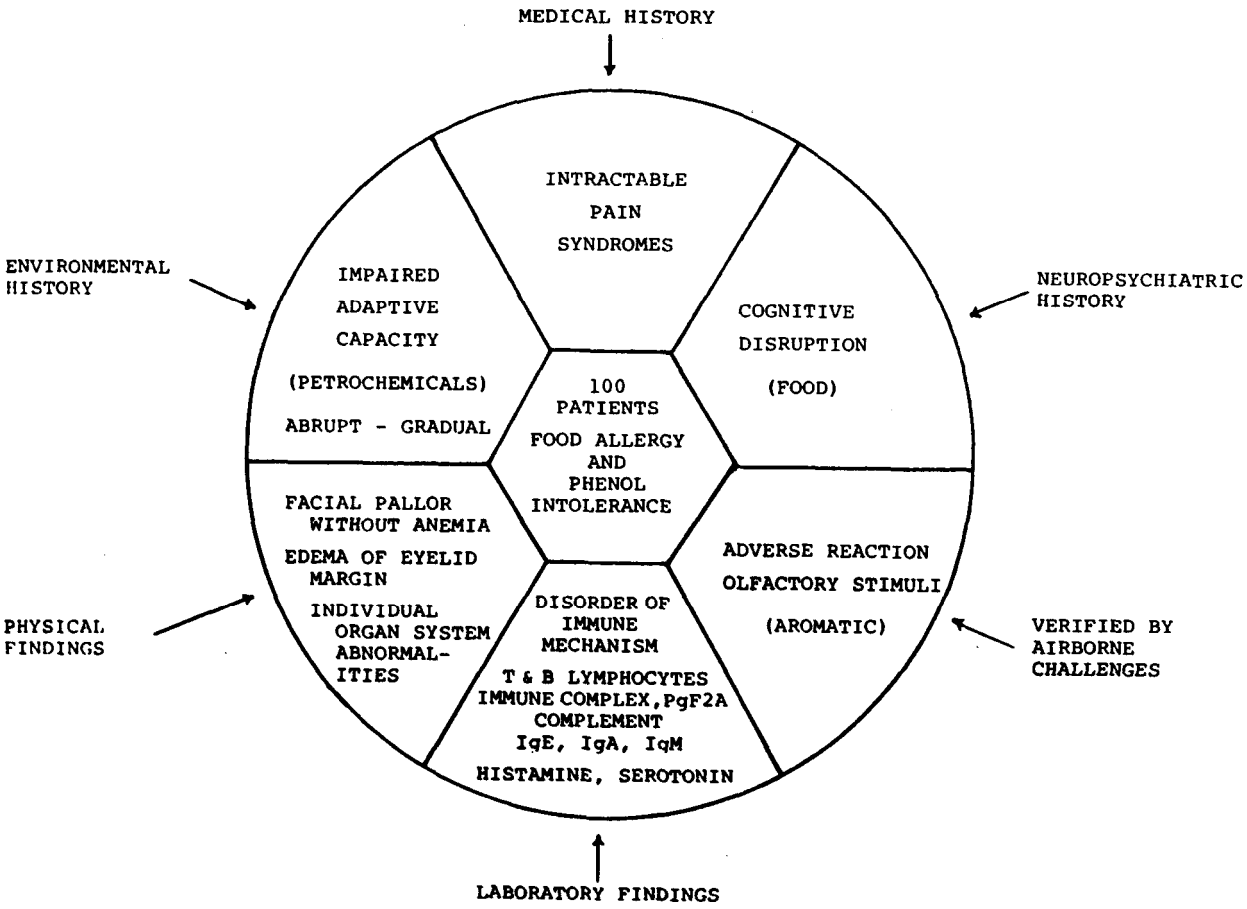

FIGURE 1. Distinctive laboratory and clinical features in patients with food allergy and phenol intolerance.

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PATIENTS WITH FOOD ALLERGY AND PHENOL INTOLERANCE
(N = 124)

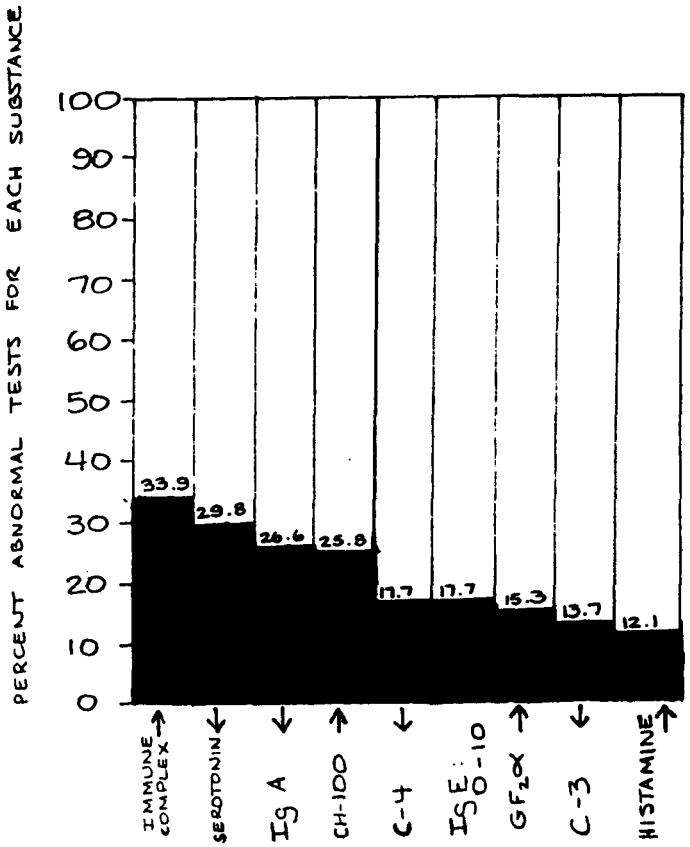

FIGURE 2: Frequency distribution of abnormal laboratory findings in patients with food allergy and phenol intolerance.

Many of the patients show evidence of immune disregulation: depressed levels of some immunoglobulin and complement factors; abnormal immune complexes (IgG) and chemical mediator levels.

Methods

Fasting blood levels of the following groups of substances were determined:

(a) the complement profile: CH-100, C-3, C-4;
(b) the immunoglobulin profile: IgA, IgG, IgM, IgD, IgE, immune complexes of the IgG type;
(c) the chemical mediator profile: serotonin, histamine, prostaglandin F2a; and
(d) the T and B cell assays: WBC and differential, total T cell count, the percent active T rosettes, total B cell count and null cell count.

Technical details for these tests may be found in Food and Chemical Sensitivity: Laboratory and Clinical Correlates; McGovern, J.J. et al., Arch, of Otolaryngology (in press).

Selection of Laboratory

Most laboratories are prepared to perform immunoglobulin and some of the complement assays. CH-100 (total hemolytic complement) is less commonly performed. Immune complexes of the IgG type are performed in only a few laboratories

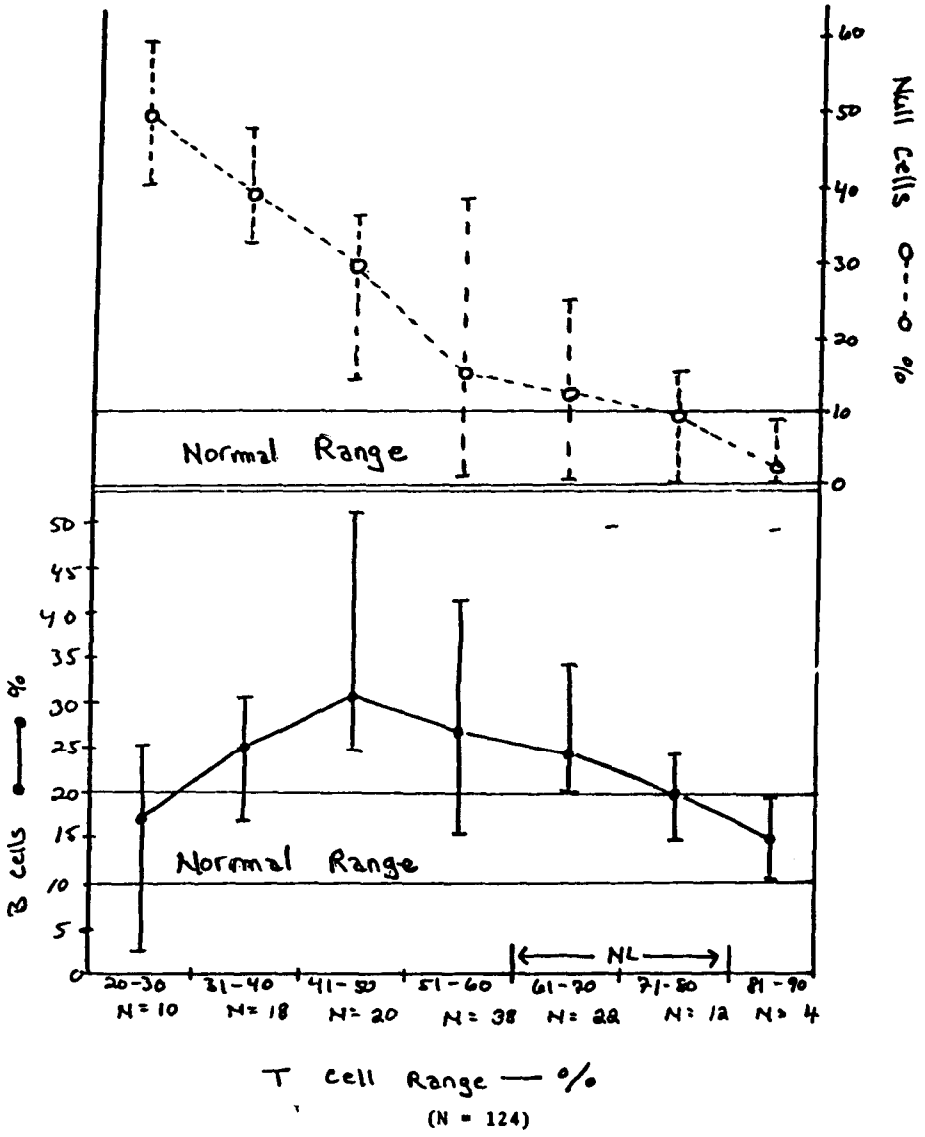

FIGURE 3: B cell and null cell levels plotted against T cell levels. Many patients had evidence of immune enhancement (decreased T and increased B cells) which is characteristic of early immunosuppression.

where arrangements have been made for this determination. Cellular assays, namely T cells and the helper and suppressor subtypes are currently performed only in laboratories providing them with an immuno-pathologist consultation. The mediators, such as PGF2A, serotonin and histamine, are done at reference laboratories. We recommend that you become acquainted with the laboratory director personally. Do this by telephone or personal visit. This will enhance your ability to use the laboratory service to support your specific needs and assist the pathologist in further development and modification of existing strategies.

Blood Samples

Blood samples should be drawn after a twelve-hour fast. We also believe that the blood should be collected in the morning between 9:00 and 10:00 to avoid diurnal variation.

Results and Discussion

The following abnormalities have been commonly observed in patients with food

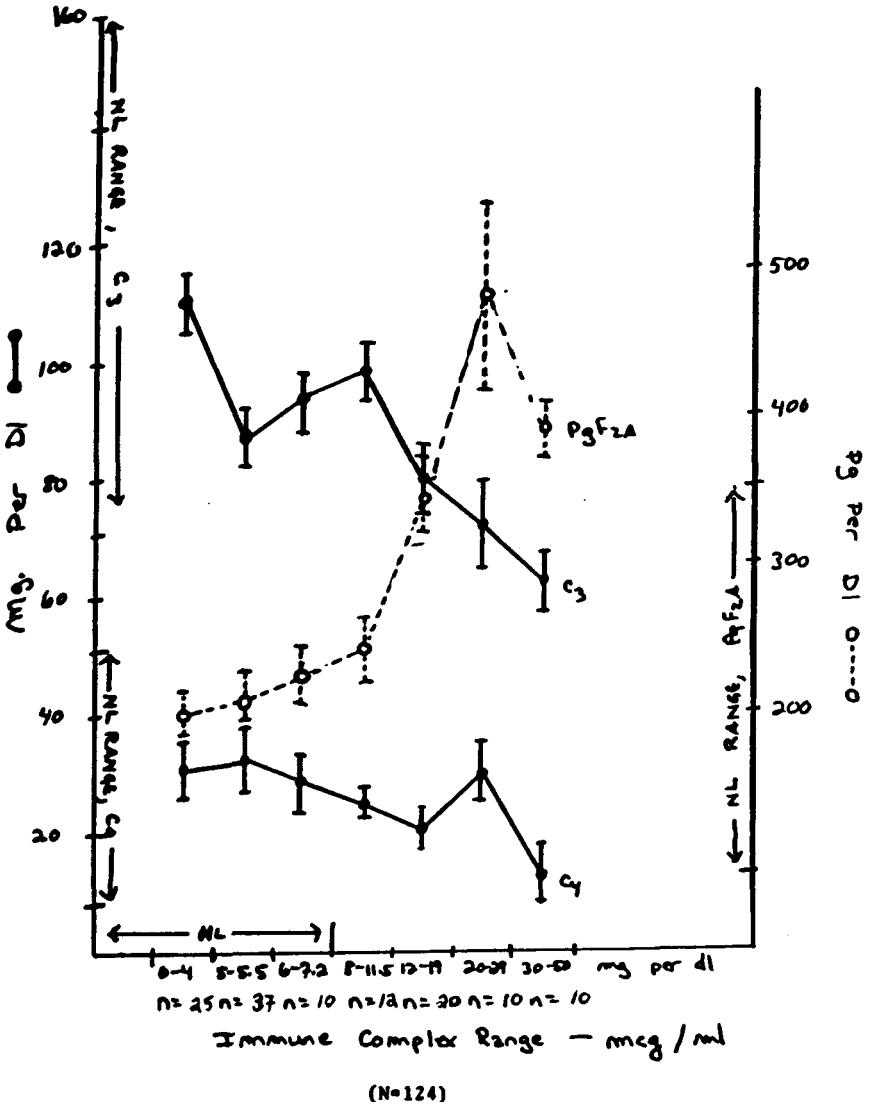

FIGURE 4: Immune complex values plotted against C3, C4 and PGF-2A. PGF-2A elevations and C3 depressions are significantly related to elevated immune complex levels.

and chemical sensitivity: (1) elevated CH-100, (2) depressed C-3, (3) very low IgE, (4) moderately depressed IgA, (5) moderate to marked elevation in the level of immune complexes of the IgG type, (6) elevated PGF2A, and (7) depressed serotonin. Each patient demonstrated at least four abnormalities.

Cellular immune abnormalities appear to be the cause of the abnormal humoral findings. We frequently see a depression in absolute T cell count. The B cell count will be elevated in the earliest stages of the process known as immune suppression. In advanced stages, however, the B cell count becomes abnormally low. We now believe that we have an explanation for this paradoxic finding. The T cells consist of two groups of cells — the "helper" and "suppressor" cells. The immune modulation function of the T cells depends on the ratio of helper to suppressor cells. The higher the ratio, the greater the stimulatory effect T cells have upon the B cells. It is commonly

understood that suppressor cells are more sensitive to damage from chemicals and other agents than are helper cells and therefore become depressed before the helper cells. This results in high helper/suppressor ratios and therefore stimulatory effects, early in immune suppression.

Recently, LaVia et al. (1979) and others (Archer, 1978; Dean and Padarathsingh, 1981) have shown that immunosuppression may occur by the deliberate exposure of healthy animals to supposedly nontoxic doses of a variety of aromatic (phenolic) compounds. These studies have illustrated that, in the very earliest stage of deliberate immunosuppression by toxic chemicals one sees a depression in the T cell suppressor cell subpopulation accompanied by an elevation in the total number of B cells. This may be associated with an increase in IgG or IgE levels in the plasma. This early phase of cellular abnormality is known as immune enhancement. Most probably, many of our studied patients with food and chemical hypersensitivity have sustained Immunotoxic damage, which has led to immune enhancement characterized clinically by almost continual allergic reactions (McGovern, 1980; Levin et al., 1981; McGovern et al., in press; McGovern et al., 1981). The pattern seen in patients with rhinosinusitus, asthma and eczema contrasts dramatically with those mentioned above. These patients usually demonstrate very marked elevations of IgE and histamine; a depression in IgG; normal IgA, complement, serotonin and T cell levels; and markedly elevated B cell levels.

INTERPRETATION OF RECOMMENDED LABORATORY TESTS

Total Complement (CH-100)
(70-150 units)

Tested by radial immunodiffusion, the hemolytic complement tests the integrity of the entire complement system. Elevated values are frequently seen when C-3 and C-4 values are normal. It may be the only complement abnormality. Patients with severe food and chemical sensitivity may have values in the range of 150-400U.

Complement Factor 3 (C-3)
(70-176 mg/dl)

A persistently low C-3 level in the fasting state is suggestive of abnormal utilization of complement and may represent a state of hypocomplementemia. Complement is activated and utilized during certain antigen-antibody reactions. Patients generating continuous antigen-antibody complexes eventually deplete complement. Diverse conditions cause persistent complex production because of a continuous supply of antigen. Bacterial endocarditis and autoimmune diseases are but a few representing diverse etiologies. We believe similar antigen production occurs in food allergy and chemical sensitivity. In many patients studied, evidence of persistent hypocomplementemia is found.

Complement factor 3 is at a pivotal point in the complement activation sequence. Activation of this component follows complement activation of either the classical or alternate (properdin) pathway. Therefore, low levels may be found in activation of one or both pathways.

Complement Factor 4 (C-4)
(16-44.7 mg/dl)

Complement factor 4 precedes factor 3 activation in the classical pathway. (The paradoxic nomenclature is a result of the chronology of the original descriptions of the components.) Its depression indicates classical pathway activation. In ecology patients, we find that any one of the components may be depressed while the others remain normal. Hence, it is good practice to consider all three tests in patient evaluation.

In summary, complement may be used as an indirect gauge of immune complex formation because most immune complexes activate complement to some degree. We have found CH-100, which is a measure of the integrity of the entire complement sequence, particularly sensitive. However, it should be remembered, CH-100 is a semiquantitative test. Hemolytic complement assays are more sensitive when determinations are made at 50 percent hemolysis.

TABLE 1. The effect of provocative challenge testing on humoral immune components. Compared to controls, many immunopharmacologic components were markedly altered following oral, intradermal and inhalational provocative challenge. Some of the abnormal clinical reactions may have been the results of an immune complex mediated vascular inflammatory reaction.

TABLE I.

CONCURRENT LABORATORY CHANGES AND CLINICAL ABNORMALITIES NOTED AFTER CONFIRMATORY PROVOCATIVE CHALLENGE TESTING

Pt. #	Substance tested	Dose Admin. DOUBLE Bl	MAJOR LABORATORY FINDINGS Prior to challenge	45 - 60 mins. after challenge LIND INTRADERMAL CHALLENGE TESTS	Abnormal findings noted at peak of clinical reaction
1	Ethanol	1 mg.	CH-100 = 230 Rast = .17/540	CH-100 = 39 Rast = 1.05/1355	Hypoventilation Loss of muscle tone
2	Cherry Extract	.1 mcg	I.C.= 13 ESR = 23	I.C. = 34 ESR= 16	Cataplectic episode
3	Cane sugar	1 mcg	C-3 = 210 ESR= 23	C-3= 120 ESR= 15	Narcoleptic episode
4	Cane sugar	1 mcg	Rast= .41/957	Rast = 1.76/2163	Acute depressive reaction Cognitive disruption
5	Formaldehyde	1 ng	PGF-2A = 195	PGF-2A= 295	Acute depressive reaction
6	Orange	4 mcg	Serotonin = 64	Serotonin = 47	Cataplectic episode
7	Orange	4 mcg	Serotonin = 117 I.C.= 10.1	Serotonin = 82 I.C.= 77.9	Hyperkinetic episode
8	Tobacco Leaf	4 mcg	B. Endorphins = 285	B. Endorphins = 154	Acute depressive reaction Cognitive disruption
9	Phenol	4 mcg	B. Endorphins = 7	B. Endorphins = 30	Hyperkinetic reaction
10	Cane sugar	4 mcg	ESR = 32	ESR = 22	Narcoleptic episode

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SINGLE BLIND ORAL CHALLENGE TESTS

11	Beef	6 oz.	I.C. = 0	I.C.= 14	Abdominal distention Migraine headache
12	Soy	6 oz.	Histamine = 0	Histamine = 12	Acute anxiety reaction, Tachycardia, Esophageal burning
13	Wheat	6 oz.	I.C. = 4 PGF-2A= 86	I.C.= 12 PGF-2A= 365	Disorientation Confusion. Mucous diarrhea.
14	Milk	6 oz.	IgG = 574 C-3= 130	IgG = 396 C-3= 75	Bloody diarrhea CNS depression
15	Potato	6 oz.	Histamine = 8 I.C.= 5	Histamine = 14.8 I.C.= 18	Abdominal tenderness Hypoventilation. Stupor
16	Red Jello	6 oz.	Serotonin = 40 I.C.= 9	Serotonin = 120 I.C.= 18	Violence Hyperkinetic episode
17	Banana	6 oz.	PGF-2A = 198	PGF-2A= 244	Hyperkinetic episode Violence
18	Corn	6 oz.	I.C. = 30 Serotonin = 70	I.C. = 90 Serotonin = 20	Swollen finger joints
19	Beef	6 oz.	CH-100 = 400 I.C. = 8 IgE= 1050	CH-100= 110 I.C.= 15 IgE = 3100	Acute depressive reaction Ophthalmoplegic migraine

SINGLE BLIND INHALATIONAL CHALLENGE TESTS

20	Phenol fumes	3ppm (5 min)	I C = 8 PGF-2A= 78	I.C. = 23 PGF-2A= 533	Acute bronchospastic episode
21	Photo-copy fumes	5 ppm (5 min)	Serotonin = 70	Serotonin = 10	Cognitive disruption Ataxia

Note: See the methods and materials for normal values and units.

IMMUNOGLOBULIN FACTORS

Immunoglobulin G (IgG)
(564-1765 mg/dl)

In the first two to five years of chronic food and chemical sensitivity, the IgG level may be normal. In patients who have had the disease for 10 to 15 years, the IgG level is often just at the lowest level or just below the lower limit of normal. In such patients we often find immune complexes of the IgG type.

Immune Complexes (0-8 mcg/l)

We have seen serum IgG levels fall following challenge. This drop is associated with prompt increase in the level of immune complexes. We are now speculating that these complexes may be of the IgG4 type. There is considerable interest in IgG4 because it, like IgE, may fix to basophils and release histamine. Very importantly, IgG4 does not or only minimally binds complement. Therefore, immune complexes of the IgG4 type cannot be detected by traditional complement binding assays such as the Raji cell test and other tests which detect Clq or C3b. Tolerogenic immune complexes are found in the sera of normal people following food ingestion. Only a laboratory testing for immune complexes by an IgG rather than a complement detection system can identify these complexes. The detection technique requires preliminary separation of complexed IgG from free IgG by polyethylene glycol precipitation followed by immunoelectrophoretic detection of precipitated IgG.

Immunoglobulin A (IgA) (85-385 mg/dl)

We found approximately 25 percent of patients with depressed IgA levels. Patients with food allergy had levels in the range of 40 to 80. IgA appears to act as a barrier to entry of macromolecular antigens into the blood via the gut. Secretory IgA is the dimeric form with a secretory component added by the gut epithelial cell. It may be assessed by submission of saliva or other gut secretion on arrangement with the laboratory director.

Immunoglobulin M (IgM) (45-250 mg/dl) About twenty percent of our patients also have abnormally high levels of IgM. We believe this identifies a particular subgroup of our patients experiencing severe interruption in bone marrow cellular maturation. It is also possible that this represents the effect of recurrent viral infections or abnormal responsiveness to Candida. Animals deliberately immunosuppressed by heterocyclic or monocyclic aromatics such as benzene, phenol, PCB, etc., initially produce IgM as immune responsiveness returns. We speculate that IgM may represent early recovery from immune system damage.

Immunoglobulin E (IgE) (14 120 I.U.)

Approximately 25 percent of our patients with food and chemical sensitivity show IgE levels of 10 LU. or below. After some of our challenge studies, we have seen the IgE levels increase as much as 500-fold. Levels above 700 LU., we have found, do not eliminate food and chemical sensitivity. High levels may represent a mingling of atopy with the patient's other abnormalities. Response to immunotherapy is often more prompt and satisfactory in patients with high IgE levels compared to patients with persistently low IgE levels.

MEDIATORS OF INFLAMMATION

Serotonin (50-200 ng/ml)

Serotonin levels are depressed in approximately 40 percent of our patients. By convention, serotonin is assayed in platelets. Thrombocytopenia and serotonin-depleting drugs such as reserpine may depress values. Prolonged attacks of severe migraine may be associated with reduced serotonin levels for 24 hours at a time.

Our studies of serial changes in serotonin blood levels following deliberate induction of type I allergic reactions demonstrate abnormal depression within 15 minutes of challenge. In controls, levels appear to increase at this time to two to three times baseline returning to normal at one hour. We speculate that low fasting levels may be the result of ongoing allergic reactions.

Histamine (3-10 mcg/dl)

Histamine is a difficult parameter to measure. Antibodies against histamine have been suggested by numerous investigators, but confirmation of their existence yet

awaits. Histamine was found elevated in 12 percent of fasting patients. We believe that this may indicate type I immune response. Serial values upon challenge have demonstrated marked elevations in values coincident with the appearance of clinical signs of rhinitis and asthma.

Prostaglandins F2A (PGF2A)
(50-359 mcg/ml)

A direct and statistically significant correlation between PGF2A levels and immune complexes have been demonstrated in our study subjects (Fig. 4). These findings establish for the first time a clinically important role for PGF2A in a disease state. Approximately 25 percent of our patients have elevated levels of immune complexes suggesting a type III reaction. Two thirds of these patients also have elevated PGF2A levels. A positive covariance of these parameters is generally observed. We speculate that following immune complex deposition, activated cell membranes release PGF2A.

BACKGROUND FOR UNDERSTANDING CELL MEDIATED IMMUNITY

T and B cells

Leukopenia and neutropenia are common findings in patients with advanced food allergy and autoimmune disease. Only more recently has lymphopenia been associated with these disorders. Depression in the level of T cells is also seen. Expected T cell levels are in the range of 1,000 to 2,000 cells per cc.

In many cases, however, we observe normal T cell values while immune suppression exists. Here, the abnormality is one involving the subgroups or subsets of the T cells — the **Helper** and **Suppressor** cells. The ratio of the helper to suppressor cells appears to be of great clinical significance. Elevated ratios (above the expected 1.8 helpers to 1 suppressor) suggest immunologic over-activity. Elevated helper/suppressor ratios are associated with non-specific B cell activation and the production of **auto-antibodies. In** these patients, it is important to **screen for autoantibodies** which may be present at subclinical levels. Depressed ratios suggest depression of the immune response.

If we can extrapolate from animal models, the presence of depressed T suppressor cells suggests a tendency for **immune enhancement** — a state of immune dys-regulation. If helper T cells are extremely depressed, the patient will show few allergic reactions and would probably not come to the clinical ecologist's office. These patients, however, are also in a state of immune dysregulation. They are at greater risk of infection, inability to eliminate virus and neoplastic cell clones (acquired immunodeficiency disease).

In the patient with severe food and chemical sensitivity, one very often finds a depression of both total T cells, and B cells. We speculate that these patients may have an abnormality in the production of lymphocyte precursors at the bone marrow level. In our experience, total T cell levels in the range of 400 per cc. are associated with extreme immune impairment. Levels in the range of 1000 per cc. are associated with moderate impairment. Levels above this may still be associated with immune dysregulation, but can be detected by the **helper/suppressor ratio.**

The use of monoclonal antibodies made available with the advent of hybridoma technology has permitted identification of helper and suppressor cells on a clinical basis. Antibodies capable of in vitro identification of these cells by fluorescent microscopy were both insensitive and non-specific. Hybridoma technology makes available clones of specific antibodies of high specificity and sensitivity. A somewhat confusing nomenclature identifying these cell lines has come into the literature. In helper and suppressor cell identification, clones named OKT4 and OKT8 respectively are used (Thomas et al., 1981; Rubin et al., 1981). Identified helper and suppressor cells are referenced as OKT4+ and OKT8+ cells respectively. Likewise, clones such as OKT11 and T101 identify the total T cell population. As the T cell population consists of just these two cell sub-populations, we would expect the sum of all OKT4+ and OKT8+ cells to equal the OKT11+ and T101+ cells. In healthy patients, agreement is within 10 percent. Close agreement,

however, is not found in immunosuppressed patients. In these patients the sum of the helper and suppressor marker-bearing cells is greater than the total bearing the T cell markers. The explanation may lie in double-marking of cells in immunosuppressed patients suggesting cellular immaturity (Cosimi et al., 1981). We hope to exploit this finding in patients as an index of T cell immaturity.

CLINICAL EVALUATION OF CELLULAR MEASURES OF IMMUNITY

Depressed WBC: There are many causes besides food and chemical allergy. Be sure to exclude viral infection etc.

Depressed WBC and depressed absolute lymphocyte count: The patient may have food and chemical allergy, bone marrow depression, toxic drug reaction or all three conditions. Investigate general medical condition carefully.

Absolute total T cell depression: Sine qua non for diagnosis of immune suppression.
800-1000: moderate
600-800: advanced
300-600: severe

Helper/Suppressor Ratio
less than 0.5/1:severe immune suppression, acquired immune deficiency syndrome ("AIDS")
1.0/1: immune suppression
1.0-1.5/1: borderline
1.6-2.2/1: normal
2.3 and greater/1: immune enhancement
(Reinherz and Schlossman, 1980; Yeys, 1982; Janossy, 1982; Yachie et al., 1981; Bach and Bach, 1981).

ROLE OF AUTOIMMUNITY IN FOOD AND CHEMICAL SENSITIVITY

We have observed that 20 percent of our patients who fail to improve after treatment by ecologic measures demonstrate anti-microsomal or antithyroglobulin autoantibodies thus establishing the laboratory diagnosis of thyroiditis. We treat these patients with suppressive doses of thyroid hormone. We have found a marked improvement and clearing of CNS symptomatology in many patients previously refractory to treatment. We are now developing a technique to identify ovarian autoantibodies in female patients who show extreme sensitivity to endogenous progesterone.

LABORATORY DIAGNOSIS OF VARIOUS CATEGORIES OF IMMUNE RESPONSE FOLLOWING PROVOCATIVE CHALLENGE

There are some circumstances in which it is important to determine the type of immune response your patient displays following allergic reaction. In such cases you will need to conduct an oral or intradermal challenge study. It may be necessary to evaluate the entire immune panel after provocative challenge. In most cases, however restudy of the most abnormal fasting tests will be sufficient. Here are examples of various combinations of abnormal results that may occur following provocative challenge:

Type I IgE Mediated Reaction (homeo-tropic) Expect to find increasing levels of histamine at 15 minutes, decreasing levels of serotonin at 30 minutes and a fall in the IgE level after one hour. Other investigators (Bellanti et al.,1981) have confirmed our findings on histamine level changes in response to challenge.

Type II IgG/IgM - Complement Mediated Reaction (heterotropic) Expect to find decreasing levels of CH-100, C-3 and C-4 in the first hour after challenge and decreases in IgG, IgM and IgA.

Type III Immune Complex Mediated Reaction Expect to find a rise in Immune Complex and PGF2A between one and two hours after challenge.

Remember that these three types of immune response are theoretical and not absolute categories. In some cases of food

and chemical sensitivity, one may see more than one pattern emerge.

If you suspect a disturbance of the neuro-immunopharmacologic system in a patient with CNS allergy, you should consider serial evaluation of these tests after one hour:

Erythrocyte Sedimentation Rate (ESR): This is a relatively stable test. Values may decrease by 10 mm or more e.g. 30 to 20 mm. after intradermal challenge. These surprising findings cause us to wonder if acute phase reactants are released in these patients.

Beta Endorphins: Marked changes in this neuropeptide have been observed following challenge. The endorphins have a known T-cell modulating activity.

Specific IgE: Following challenge by unrelated food phenolic and other chemical agents, marked elevations in a wide array of specific IgE's detected by RAST have been observed.

CONCLUSIONS

1. Patients with food and chemical hypersensitivity have definite laboratory abnormalities.
2. Fasting blood samples demonstrate a high incidence of immune complexes, complement and mediator abnormalities.
3. A high incidence of T and B cell abnormalities are found. The abnormalities suggest an acquired immunosuppressive pathogenesis.
4. The abnormal immunologic changes which follow challenge testing may be correlated with the clinical result. Some of the abnormal clinical reactions may have been caused by an immune complex mediated vascular inflammatory reaction.
5. Immune dysregulation is a co-participant in many syndromes presenting primarily as psychiatric disturbances. Patients presenting with psychiatric complaints should undergo an evaluation of their immune system.

Acknowledgements

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