Controversy Over Multiple Chemical Sensitivities

To the Editors: Simon and associates (1) state that their findings “militate strongly” against a role for the immune system in the pathogenesis of multiple chemical sensitivity. Although we commend the authors for the intent and design of their study, we believe that their laboratory data do not militate for or against this conclusion.

First, the use of the term “titers” in the abstract is misleading because only the presence or absence of the five autoantibodies was reported. The importance of these antibodies cannot be assessed without full titration of positive specimens.

Second, fluorescence microscopy, used for detection of surface antigens on lymphocytes, is imprecise and inaccurate compared with flow cytometry. The latter is much more sensitive and objective than the naked eye and can count many more cells (typically 2500 to 10,000 per sample, compared with a few hundred at most by microscopy). The use of flow cytometry is especially important for measurement of scarce, dimly fluorescent cells such as peripheral blood lymphocytes expressing CD25 or CD26. For these reasons, the phenotypic analyses presented are not informative.

Third, the study of immune measures is in no way exhaustive. It remains possible that other unexamined antibodies, lymphocyte populations, or immunologic functions (which can be abnormal without changes in cell members) were altered. The authors recognize this, but their argument that the battery of tests “included all those recommended for evaluation of chemical sensitivity by a laboratory prominent in this area” is undemonstrative, given the anonymity of this laboratory and the limitations of the tests done. Finally, the article lacks important technical information regarding methods and controls, and misstates cell concentrations in the peripheral blood.

The authors may be correct that the immune system does not play a role in multiple chemical sensitivity, but the laboratory methods used in this study lack the power to test this hypothesis. What the article does support unequivocally is the need for appropriate laboratory procedures and more critical review of articles submitted for publication.

Joseph B. Margolis, MD, PhD
Johns Hopkins School of Hygiene and Public Health
Baltimore, MD 21205

Robert F. Vogt, Jr., PhD
Centers for Disease Control and Prevention
Atlanta, GA 30333

References

To the Editors: The article by Simon and colleagues (1) on multiple chemical sensitivity reported an absence of significant immunologic abnormalities in the study patients. This conclusion was based on autoantibody testing combined with an analysis of lymphocyte subset numbers and function.

We have seen at least three patients with multiple chemical sensitivity associated with IgG subclass deficiency, specifically, a lack of IgG2 or IgG3. Because IgG2 subclass, IgA, and complement deficiencies have each been associated with asthma and recurrent upper respiratory infections that may mimic chemical sensitivity (2-4), failure to test for such deficiencies significantly weakens the study. If the authors have banked serum from their patients and controls, perhaps this deficiency could be remedied.

Raphael B. Stricker, MD
California Pacific Medical Center
San Francisco, CA 94120

References

To the Editors: Simon and coworkers’ (1) conclusion that psychological symptoms are a central component of multiple chemical sensitivity is warranted by their data. By their own admission, “more than one half of the cases did not fulfill criteria for any current psychiatric diagnosis, and almost 25% showed no evidence of clinically significant psychological distress.” Further, their estimate of 25% as the percentage of patients with “somatization disorder” is questionable because the Diagnostic and Statistical Manual of Mental Disorders (third edition, revised) definition for “somatization disorder” is recursive: Distinguishing between physical and psychological ailments is prerequisite knowledge. We may conclude from Simon and colleagues that (1) a heterogeneous group of predominantly female patients exists who persistently complain and for whom physicians are unable to make any definitive diagnosis (much to the annoyance of physicians who feel that their competence is challenged and their time wasted); (2) certain immunologic tests do not distinguish patients with putative multiple chemical sensitivity from other patients; (3) some patients with multiple chemical sensitivity suffer psychological disorders that may warrant further investigation and treatment that may not relieve their physical complaints; and (4) physicians use psychiatric diagnoses as a default when they do not know what to do with patients who persistently complain.

Matti Caze
Baton Rouge, LA 70806

References

To the Editors: How can we, as readers, have confidence in this journal when it publishes the article by Simon and colleagues (1) discussing factors of multiple chemical sensitivity? They receive grants from the Boeing Company, which must have a huge vested interest in disproving the existence of multiple chemical sensitivity. Please explain how this is unbiased.

Robert D. Byers, MD
Internal Medicine Associates
Santa Barbara, CA 93105

References

1 February 1994 • Annals of Internal Medicine • Volume 120 • Number 3 249
To the Editors: As a physician disabled with multiple chemical sensitivity, I read with trepidation the article by Simon and colleagues (1) and the accompanying editorial (2).

Although I applaud the authors for attempting to examine the role of immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity, a possible conflict of interest and bias in the study design make their lack of positive immunologic and neuropsychological findings suspect. First, the study was sponsored in part by the Boeing Company, which has a huge vested interest in disproving the existence of multiple chemical sensitivity as a "real" illness. Many former employees in Boeing's Washington State plants have pending workers' compensation lawsuits alleging disability from exposures to workplace chemicals.

Another problem is defining patients on the basis of a diagnosis of chemical sensitivity in their chart. No criteria are listed for how the diagnosis was made. The wide spectrum of disease among chemically sensitive patients means that even selecting persons with symptoms in at least three organ systems and who report sensitivity to four or more substances (as Simon and colleagues did) will still mix patients who are mildly, moderately, and severely ill. This may have diluted the findings because only the most severely ill might have shown test abnormalities.

Mixing the laboratory values also presents a problem in interpreting the cellular immune studies because values above and below the normal range cancel each other and make it appear that no abnormalities are present. Other studies have shown that chemically sensitive persons often have immune abnormalities that differ from those of other persons with multiple chemical sensitivity (3-5).

Another source of ambiguity involves the analysis of symptoms that are said to have occurred before or after a finite event called "the onset of chemical sensitivity." Can the exact onset of chemical sensitivity ever be known? Although some people with multiple chemical sensitivity report being totally healthy one day and extremely ill the next, most chemically sensitive persons experience declining health (which can last from several hours to years) punctuated by significant worsening.

Further, the term "somatization disorder" is a useless and misleading label given to persons with many physical symptoms not explainable by a known medical condition. It is a psychiatric diagnosis only by default. Still, the authors found that almost 25% of case patients showed no evidence of clinically significant psychological distress and that the presence of psychological symptoms in other patients did not predate the onset of chemical sensitivity.

My final complaint about this paper is that the discussion of the use of strict avoidance regimens for the treatment of multiple chemical sensitivity is inappropriate, given that the authors admit that their study did not address this issue. They still go on to state that the "benefits of severe avoidance do not justify the accompanying disability and isolation." This unsubstantiated speculation goes far beyond the scope of their study.

Ann McCampbell, MD
485 Hot Springs Road
Santa Barbara, CA 93108

References

To the Editors: Simon and colleagues (1) appear to present a case-control study comparing chemically sensitive patients with controls without specific and measurable prestudy hypotheses. The results are useful only to develop recommendations for future studies, and only if the study was done adequately. However, flaws in participant selection and the information collected probably biased their results.

Simon and colleagues selected patients with a computer billing code of multiple allergy, and then screened for illness lasting 3 months or more, multisystem involvement (including the central nervous system), and self-report of sensitivity to chemicals. With no screening for length, type or severity of exposure, level of sensitivity, or degree of illness, confounding variables remain unaddressed. Controls were not selected for sensitivity to chemicals, masked regular exposures, or previous occupations that could have provided chemical exposures. Bell and colleagues (2) report that in a random group of 643 college students, 15% report symptomatic response to chemicals. Musculoskeletal and back injury occur predominantly in "blue collar" occupations such as manufacturing, where chemical exposures are common.

Cases and controls were then matched for age, sex, and educational level, insufficient criteria that may have missed important factors. We argue that dilution of cases and controls through systematic error in participant selection, combined with a poor response rate and small sample size, severely blunts the results of this study.

Diagnosing mental illness when patients are known to have central nervous system dysfunction and multiple symptom systems is difficult. A presupposition of a healthy central nervous system exists in measures of depression and anxiety. Where patients with central nervous system dysfunctions exist, these measures are less valid. The validity of the somatization scale is lowest of all Diagnostic Interview Schedule measures (3). Using this diagnostic tool on a group of patients with variable multiple symptom systems and unclear cause only emphasizes inherent problems with validity.

Research has shown memory impairment in persons exposed to chemicals who were chosen under careful criteria (4) and brain damage with related emotional and functional disruption from exposure to chemicals (5). For future study of environmental sensitivity, development of clear classification systems and identification of confounding variables should be priorities.

Jacqueline Krohn, MD
Jill Ryan, BA
Julie Jacobson, PhD, MS, RN
Los Alamos Medical Center
Los Alamos, NM 87544

References

In response: Drs. Margolick and Vogt raise questions about the comprehensiveness of the immunologic battery and the accuracy of specific laboratory techniques. We agree that more extensive and more technically sophisticated evaluation might be preferable. Our choice of immunologic evaluation was pragmatic. We used the expert "panel of studies typically done by environmental physicians for assessment of chemically sensi-
tive patients and on which a diagnosis of multiple chemical sensitivity is often based. Although these data may have some limitations in the study of immunologic mechanisms, they clearly argue against the utility of immunologic assessment as currently practiced.

We thank Dr. Stricker for his suggestion regarding IgG subclass, IgA, and complement testing, and may pursue it.

Drs. Krohn and Jacobson and Ms. Ryan raise questions about selection of cases and controls. We can address the three specific issues raised. As stated, controls were screened for symptoms of chemical sensitivity, and two patients were excluded. Controls were not, however, screened out because of previous chemical exposure. To do so would have been inappropriate in a study designed to assess the relation between chemical sensitivity and chemical exposure. Although research psychiatric interviews have important limitations, we do not agree that research on chemical sensitivity should ignore the domain of psychological distress, given previous research. Their other concerns regarding confounding, bias, and failure to match on "important factors" are too vague. Extensive data were collected on exposure history, occupational history, and severity of illness, and we would be happy to respond privately to more specific questions.

We appreciate Ms. Cox's point that for a significant minority of patients with multiple chemical sensitivity, psychological symptoms are clearly not "central."

Both Dr. Byers and Dr. McCamphell question how funding from the Boeing Company may have influenced our research. Partial support for laboratory expenses was provided by the International Association of Machinists/Boeing Health and Safety Institute. This institute is operated jointly by Boeing and its largest union to promote research and education in occupational health. Grants for independent research are awarded after review by a committee of labor and management representatives. Given the controversy surrounding chemical sensitivity, we argue that representation of both workers and management minimizes the potential for bias.

Dr. McCamphell questions whether immunologic findings might have differed if analyzed according to severity of chemical sensitivity or according to the proportion of patients with abnormal results. Neither of these approaches produces a different picture. More severe chemical sensitivity was not associated with greater immunologic abnormality and the two groups (cases and controls) did not differ significantly in the proportion of patients with abnormal findings (using laboratory reference standards). As for the dating of previous symptoms, we agree that recall of remote symptoms is imprecise, but recall is the only available measure. Our analyses were based on patients' own reports of the onset of chemical sensitivity and of individual symptoms.

Finally, we stand by our comments regarding avoidance. Our intent was to highlight the lack of evidence supporting avoidance of low-level chemical exposures. To date, no controlled studies show any physiologic injury in chemically sensitive patients that might be exacerbated by low-level chemical exposure. In our opinion, the disability and isolation caused by avoidance regimens argue strongly for a rehabilitative approach.

Gregory Simon, MD, MPH
Center for Health Studies
Seattle, WA 98101

William Daniel, MD, MPH
University of Washington
Seattle, WA 98195