A Novel Treatment for Fibromyalgia Improves Clinical Outcomes in a Community-Based Study

Patricia A. Deuster
Russell M. Jaffe

ABSTRACT. Objectives: Immunoreactant load was assessed by using lymphocyte response assay [LRA] with cell response/blastogenic mixed cell culture to determine if substitution of reactive items would be associated with remission of symptoms in subjects with fibromyalgia syndrome [FMS].

Methods: Fibromyalgia subjects [N = 51] were assigned to a control [C: N = 11] or treatment [T: N = 40] group; C maintained usual life-styles and T, after LRA testing, underwent a program of substitution and nutritional repletion with metabolic intermediates. All subjects participated in biweekly support groups and completed questionnaires [0 months, three months, and six months] to document changes.

Results: After six months T experienced 50% less pain, 70% less depression, 50% more energy, and 30% less stiffness, whereas C reported an increase in pain and depression, and comparable levels of stiffness and energy as compared to pre-program levels.

Conclusions: These data suggest that reducing the immunoreac-

---

Patricia A. Deuster, PhD, MPH, Associate Professor, is affiliated with Health Studies Collegium.

Russell M. Jaffe, MD, PhD, is affiliated with Health Studies Collegium, and Director and CEO, Serammune Physician's Laboratory.

Address correspondence to: Russell M. Jaffe or Patricia A. Deuster, Health Studies Collegium, 1890 Preston White Drive, Reston, VA 22091.

Funds for this study were awarded to the Health Studies Collegium by The Huston Foundation of West Conshohocken, PA.

Submitted: May 16, 1996.

Revision accepted: February 7, 1997.

tant load in FMS, while stimulating repair, may help re-establish homeostasis and neuroimmune hormonal control. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworthpressinc.com]*

KEYWORDS. Affective disorder, clinical protocol, colonic diseases, fibromyalgia, immunoactivators, food and environmental sensitivity

BACKGROUND

Fibromyalgia syndrome [FMS] is an increasingly common diagnosis of unknown etiology whose pathophysiology is still poorly understood (1-3). Since 1990, when the American College of Rheumatology [ACR] published classification criteria for FMS (4), it has been shown that FMS is quite prevalent [5-10%]; women account for more than 70% of the diagnoses (5,6). Several suggestions have been made concerning FMS's etiology, including abnormalities in central nervous system neurotransmitter concentrations (7-12) [especially vasoneuroactive amino acid metabolites like serotonin (12)]; neurohormonal dysregulation [including adrenocorticotropic hormone, growth hormone, vasopressin and oxytocin (3,13-16)]; disorders of non-rapid eye movement sleep (17); muscle metabolic and energetic dysfunction (18); and reactive psychopathology (19). Despite numerous hypotheses, no consensus has yet emerged. Yunus (14) recently expanded his hypothesis that there is a *heterogeneous neurohormonal dysfunction* with resultant aberrant pain mechanisms, fatigue, and disorders of sleep. These dysfunctions may be intensified by stressors, trauma, poor posture, and environmental stimuli.

One central theme that integrates all bodily systems is a dysfunction in the neuroimmune hormonal [NIH] feedback-controlled system. Recently, several immunologic dysfunctions have been identified in patients with FMS (3,20-24). In particular, FMS patients have been shown to have lower natural killer cell activity (20-22) and altered interluekin-2 (23) secretion as compared to asymptomatic control subjects. Some investigators report deposits of immunoglobulin G [IgG] at the dermal-epidermal junction in skin biopsies from FMS patients (24). These findings demonstrated a need for investigations into the role of immunologic load on NIH function and on the functional integrity of the human immune defense and repair systems.

Consistent with the work of others (9-12,14), we hypothesized that an

intervention to interrupt immunoreactant exposure would restore homeostasis to the NIH system. To test this hypothesis, a detailed assessment of individual responses to a relevant variety of common possible immunoreactants was required. A high-sensitivity lymphocyte response assay [LRA], mixed-cell culture was used to identify delayed hypersensitivity Types II [humoral/antibody], III [immune complex], and IV [cell-mediated immunoreaction] reactions to up to 350 items [including controls, common medications, foods and food additives, as well as environmental chemicals and toxins]. The results of this LRA were used to establish a program of systematic substitution. This clinical treatment guideline was designed to reduce the proposed immunotoxic hyperstimulation that the hypothesis suggests is integral to NIH dysregulation.

MATERIALS AND METHODS

The study was approved by the Human Use Review Committee of the Health Studies Collegium [HSC]. Subjects were recruited by word of mouth and physician referral. Those who met the diagnosis of FMS by standard ACR criteria (4) were invited to participate. The diagnosis of FMS was made on all volunteers by one physician not connected with the study. The physician manually palpated each of the 18 tender point sites and recorded the number of sites meeting the designated criteria for FMS. The requirements of being in the treatment [T] group and the overall nature of the study were explained in detail. As a result of the requirements, some subjects specifically requested to serve as controls; other subjects were randomly assigned to groups. All persons in the control [C] group were assured they could undergo the treatment program at the end of the six month program if they so desired. Thus, group assignment was not random. In the end, 11 subjects were assigned to the C and 40 to the T group. A greater number of subjects were assigned to the T group because a greater drop-out rate was anticipated. A drop-out rate of 25% was expected based on experience with other community based outcome studies.

After providing informed consent, all subjects completed a questionnaire designed to obtain information relating to duration of symptoms, symptoms relating to a precipitating event, types of health professionals seen for symptoms, concurrent illnesses, medications taken, severity of pain, global disease severity, and specifics with respect to their symptoms. Subjects were given a picture of the human body with ventral, dorsal, and lateral views; they were instructed to place, on clearly designated sites, a number ranging from 0 to 100 [0 = no pain and 100 = extreme pain] to denote the intensity of their pain. A total pain score was obtained by

summing the numbers written on the specific sites of the picture [maximum score = 1500]. Information on global assessment of FMS and symptoms was obtained by having subjects rate specific symptoms on a scale of 0 [none] to 100 [severe]. The symptoms questionnaire had been structured to gather information according to the criteria for responses outlined by Simms et al. (25), and included symptoms such as disturbed sleep, morning stiffness, muscle pain, lack of energy, rhinitis, migraine headaches, muscle tremors, irritable bowel, temporomandibular joint pain, facial pain, stress, anxiety, and depression. Specifically, the subjects were asked to rate each symptom on the questionnaire that they experienced *within the last week* in an effort to obtain more accurate reports. These outcome questionnaires were completed again at three and six months by both C and T subjects. After completing the study, FMS patients were further subdivided based on their histories and manifestations during the study as being either primary FMS or having FMS plus other concomitant disease. This group was designated as FMS Plus subjects. FMS Plus subjects consisted of those who exhibited multiple illnesses such as chronic fatigue syndrome, irritable bowel syndrome, arthritis, Lyme's disease and/or diabetes.

After completing the questionnaires, T subjects were scheduled for a blood draw. Whole blood [1 ounce; 27 ml] was drawn from all subjects in the T group for the LRA. The LRA immune test by the enzyme-linked immunosorbant assay/activated lymphocyte cytotoxicity test [ELISA/ACT] method combines lymphocyte enzyme activation with cell response/blastogenic mixed cell culture. The Immune Cytotoxicity Test [ICT] is another blood test which purports to assess reactivity to various antigens, toxins, and metabolic poisons (26,27). However, the ELISA/ACT LRA should not be confused with the ICT: the ICT uses whole blood and thus the endpoints are neutrophil, platelet and erythrocyte fragments, whereas the ELISA/ACT LRA uses lymphocyte recognition of epitope as the reaction trigger and kinase-associated blastogenesis as the reaction endpoint.

Blood for the ELISA/ACT test was drawn using a two-syringe technique [as described by Jaffe and Deykin (28)] suitable for functional lymphocyte response assays. Standard procedures are followed before having blood drawn for the ELISA/ACT test; these include asking patients to discontinue steroids for four days and aspirin and antihistamines for two days prior to the phlebotomy, and fast for 12 hours overnight. This precaution is taken to avoid interferences with cell membrane responses. In this group of subjects, none were taking steroids. Subjects reported for the blood draw in the morning after having ingested only water.

Subjects in the T group received the results of their blood tests, and based on the results of this test, a detailed dietary modification program

was provided at their first biweekly support group meeting. The dietary programs were individualized to conform with their specific food/environmental reactivities. For example, a person with a reaction to wheat would be required to eliminate all products containing wheat and wheat-derived as well as wheat-related antigens from his/her diet for the six months to follow. Someone with a reaction to sulfites would be instructed to substitute all sources to the extent possible. Although foreign reactants are present in only trace amounts, the primary immune defense and response system is a low capacity, variable to high specificity, high amplification system when compared with the high capacity, low specificity and amplification of the immune surveillance phagocytic/dendritic cell system. Thus, even a small amount of an item that evades neutralization and induces a re-activation in a hyperstimulated immune system may persist or enhance symptoms dependent or derivative of the results of such reactions.

Information and Support Groups. All subjects attended biweekly support group meetings. Subjects in the T group discussed problems and posed questions about the treatment guidelines with their group leader, e.g., how to eat healthfully or how to substitute for reactants competently. Subjects in the C group met with the same group leader on weeks alternating from the treatment group to discuss various issues with respect to FMS.

All T group participants took a variety of supplements on a daily basis: these included full spectrum antioxidants, buffering minerals, metabolic intermediates, and necessary cofactors [a complete breakdown of the supplements will be provided upon request]. Although individualizing supplements would have been preferred, this was deemed untenable due to lack of appropriate control. The supplements were provided to ensure availability of all cofactors and other metabolic intermediates requisite for immune function and repair. Subjects in the control group were not given additional supplements although they were encouraged to continue taking whatever they may have been taking; three C subjects were taking supplements. The support group and treatment program was followed for six months.

Immune Testing Procedure. Blood samples were maintained between 4-10°C during transport and prior to cell culture. Whole blood was centrifuged [$980 \cdot g^{-1} \cdot min^{-1}$] to obtain a cell rich plasma [CRP] supernatant; the CRP was aspirated into a standard polyethylene transfer trough and aliquotted [45 µl/well] at room temperature into precoated microtiter plates [48-6 mm diameter, 1 mm deep wells/plate] and then placed in

humidity controlled incubation chambers for incubation at 35 ± 1°C for three hours.

Samples were read using a light microscope equipped with 40 × LWD [long working distance] lenses and 15 × UWF [ultra wide field] occulars. A sample was considered to be moderate in reactivity if 25-50% of the lymphocytes showed activation. Strong reactivity was recorded if >50% of the lymphocytes showed activation. A minimum of five fields/well was read and the results were averaged. Active cells showed symmetric and a substantial increase in the spherical volume of the glycocalyx; this is presumed to be linked to kinase activation at the major histocompatibility locus in the human lymphocyte membrane. When cells exhibited asymmetric apparent increases in cell volume or appeared as pyknotic cells, they were classified as false positive reactions and ignored. Results vary <5% day to day on split samples from the same individual on a constant diet/activity program. Control substances were interspersed throughout the panel to document the accuracy of the procedures and whether subjects had followed instructions for the blood draw. Blood samples were analyzed for 350 antigens [a complete list of all antigens tested will be provided upon request]. The primary categories of substances included environmental chemicals, food additives and preservatives, crustaceans, dairy products, fish, fruits, grains, meats, molluscs, oils, and other groups. Within each category was a variety of collateral epitopes or "antigens" considered essential for full interpretation. Currently, the only validation for the ELISA/ACT LRA is based on multiple replicates on individuals over time, split sample data [blinded], and numerous case studies; other prospective outcome studies are in progress. Comparing ELISA/ACT LRA results with results from skin tests and concurrent double blind food challenge awaits future studies.

Antigens [purchased from either Pharmacia, Inc. Allergen Division; Sigma; or Aldrich] for the 350 substances were processed and extracted using standard protein chemistry techniques for antigens, haptens, glyco/lipopeptides, polysaccharides, and hydrophilic/hydrophobic substances. The final concentration of substances was standardized at 0.01 μM, sufficient to coat a monolayer on the optical surface of the microtiter well used as the cell culture chamber. Extracts, in suitable volatile buffer for coating both hydrophilic and hydrophobic substances onto the styrene microtiter surface, were prefiltered to eliminate material in excess of about 10^7 daltons as such material is well above the physical uptake maxima of even a hyperpermeable human intestinal tract. Extracts of antigen solution were aliquotted [25 μl/well] using a Sandy Springs Instrument Company multipipettor; this amount was sufficient to homogeneously coat the plate sur-

face. Plates were then dried in oven racks for 24 hours; filtered air at 23 ± 2°C and ambient pressure was used.

Statistical Analyses. Means and standard errors of means were calculated. To determine differences between groups, data were analyzed as a two factor, repeated measures analysis of variance: the two factors were time and group [T versus C]. The statistical analysis package General Linear Models [SAS] was used, and this approach adjusts for missing values and unequal sample sizes. The Duncan's Multiple Range test was used to ascertain differences among groups when significant main effects were noted. Because of the wide range and variability in the responses, data were expressed as a percent of the baseline, or initial, response. Changes across the third and sixth months were compared to responses at the beginning of the study. Although we selected a P value of 0.05 as significant, when multiple tests were being performed, the P value was adjusted for the number of tests to reduce the chances of making a Type I error.

RESULTS

A total of 51 subjects were recruited [11 in the C group and 40 in the T group], but complete sets of questionnaires were obtained for only seven Cs, 13 FMS and 12 FMS Plus subjects. The subject characteristics for those enrolled in the study are presented in Table 1. Despite the lack of complete random assignment, the only difference between the C and T groups was age: the C group was slightly older. In contrast, those who dropped out were more likely to have had FMS for a longer period of time. For drop-out subjects, the C and T subjects have been pooled. The signifi-

TABLE 1. Characteristics of the Fibromyalgia Groups

Variable	Controls N = 7	Primary FMS N = 13	FMS Plus* N = 12	Drop-out Subjects N = 19
Age [yrs]	54 ± 3	48 ± 2	41 ± 2	45 ± 2
Gender [# Female/Total]	7/7	13/13	11/12	20/20
Duration of Pain [months]	73 ± 22	77 ± 13	78 ± 20	92 ± 20
Tender Spots [#]	14 ± 1.0	13 ± 0.5	14 ± 0.6	14 ± 0.6

*Chronic fatigue syndrome, reflex sympathetic dystrophy, multiple chemical sensitivity, irritable bowel syndrome, arthritis, Lyme's disease and/or diabetes.

cance of this difference in terms of data analyses is unclear. Interestingly, 72% of all subjects reported a specific precipitating event, such as a car accident, a fall, or the flu. The most common medications taken by the subjects included Zoloft, amitriptyline, hormone replacement therapy [premarin, estrogen], and non-steroidal anti-inflammatory agents.

Some T subjects were dropped [N = 4] because they sought medical care for other health problems during the study and did not stay on the regimen. The data for the other 11 subjects are not presented because they failed to complete either the three month or the sixth month questionnaire; there were a variety of reasons for not completing the questionnaire including, moved [N = 1], lived too far away to attend support group [N = 2], or had serious personal or family problems [N = 2]. Although this is a concern, adhering to the program requires commitment and dedication. Thus, the drop-out rate is not surprising.

Table 2 presents the frequency of positive reactions to the blood testing for the 40 subjects who had the test. All of these FMS subjects had multiple food/environmental sensitivities: the subject with the smallest number had 15 intermediate to strong responses and the one with the highest had 32 positive reactions. Thus from 4 to 10% of substances tested were found reactive in the cell culture. Table 3 presents the overall results of the items found positive with blood testing. The most frequent reactive substance was the commercial flavorant monosodium glutamate/MSG,

TABLE 2. Number of Positive Reactions to Immune Testing

Number of Subjects	Number of Positive Reactions
1	15
1	16
1	19
3	20
1	21
2	22
5	23
2	24
3	25
1	26
1	27
5	28
3	30
2	31
1	33

TABLE 3. Frequency of Positive Reactions to Foods, Food Additives, Environmental Agents, and Other Chemicals

Substance	Proportion of Reactions [%]
Monosodium Glutamate	42.5
Candida albicans	37.5
Caffeine	37.0
Chocolate/Cocoa	37.0
Food Colorings	37.0
Cola Beverages	37.0
Shrimp	37.0
Cow Dairy Products	25.0
Sulfite/Metabisulfite	22.5
Xylene	22.5
Yogurt	22.5
Aspartames	20.0
BHA	20.0
Cadmium	20.0
Lead	20.0
Tylenol	20.0
Yeast [*C. albicans*]	20.0
Sodium Benzoate	20.0
Orange	20.0

followed by *Candida albicans*, caffeine, food coloring, chocolate, shrimp, and dairy products. In no case were any of the items used as controls in the test battery positive. In fact, if the response to a control item/reagent was reactive, the blood was redrawn and the entire test redone; a positive response to a control item indicates non-specific lymphocyte activation. This usually indicates that patient preparation and phlebotomy procedures have not been followed as specified. Previous work in our laboratory [unpublished data] indicates that "healthy," normal, control subjects show only rare reactions, the most common being cow's milk, corn, and butylated hydroxytoluene [BHT]. These observations are consistent with the frequency of consumption of these items [and processed derivatives thereof] in the diet's of most individuals studied for whom data are available.

Analysis of the self-rated symptom questionnaires revealed a number of

differences between the C and T groups. Table 4 presents the results of selected symptoms and overall scores for the three periods of observation. All scores have been normalized for baseline values. As noted in Table 4, the pain score was greater in the Cs at months three and six [more than 50% as severe] as compared to the T groups [less than half as severe]. In absolute numbers, pain scores at the beginning of the study averaged 873 ± 117 for primary FMS treatment group subjects; 938 ± 126 for FMS Plus treatment group subjects, and 543 ± 157 for C subjects; the highest possible score for the 15 body tenderness sites was 1,500. These differences were not significantly different. Those with primary FMS experienced 50% less pain at the end of the six months than at the start of the program. Those with FMS Plus also experienced a significant decline in overall pain, but to a lesser degree than primary FMS subjects. In contrast, Cs reported an increase in pain [2/7].

With respect to other specific symptoms, primary FMS and FMS Plus scores for depression at the end of the study were 70% and 10% less than at the start of the study, whereas Cs scores were 25% higher. Similarly, rhinitis score were significantly lower [40%] after completing the program as compared to the start. No change in rhinitis score was observed for Cs or FMS Plus [Table 4]. Sleep disturbances were reduced in all groups as a function of time: six-month values were 48.1 ± 8.1%, 78.2 ± 11.1%, and 70.0 ± 11.2% of beginning values for primary FMS, FMS Plus, and C subjects, respectively.

Other symptoms of interest were morning stiffness, lack of energy scores, and complaints of irritable bowels [Table 4]. By the end of the program, primary FMS subjects experienced reduced stiffness [30% less], and reported greater energy [50% more] than they had experienced prior to starting the treatment program. In contrast, control scores at the end of the six months were 100% of what they reported at the beginning of the study for both stiffness and lack of energy. Again, improvement for the FMS Plus was noted but to a lesser extent than seen for those with primary FMS. Relative to irritable bowel symptoms, primary FMS patients scored at least 50% lower after six months as compared to before the start of the program. In contrast, no change in these complaints were noted by Cs or those classified as FMS Plus. Table 4 also presents the average change in symptoms score, which was calculated by summing the change scores for all symptoms. An improvement [noted by a lower score] was observed for those with primary FMS. From a relative score of 1.0 at baseline, overall symptom reduction averaged 45% less for those with primary FMS. These overall improvements were not seen in C or FMS Plus subjects.

Lastly, subjects rated their overall health on a scale from 1 to 100, with 1

TABLE 4. Self-Reported Changes in Selected Symptoms, Average Symptoms, and Overall Health at Three Months and Six Months, Expressed as a Percent of Baseline

Group	Three Months	Six Months
	Pain Scores	
Control	1.23 ± 0.40	1.60 ± 0.45
FMS*	0.46 ± 0.08	0.36 ± 0.10
FMS Plus	0.68 ± 0.19	0.61 ± 0.13
	Depression Scores	
Control	0.65 ± 0.25	1.27 ± 0.66
FMS	0.52 ± 0.10	0.38 ± 0.09
FMS Plus	0.91 ± 0.15	0.97 ± 0.24
	Rhinitis Score	
Control	0.94 ± 0.40	1.13 ± 0.44
FMS	0.61 ± 0.09	0.51 ± 0.09
FMS Plus	1.07 ± 0.24	0.98 ± 0.15
	Sleep Score	
Control	0.63 ± 0.11	0.70 ± 0.11
FMS	0.61 ± 0.08	0.48 ± 0.08
FMS Plus	1.00 ± 0.11	0.78 ± 0.11
	Stiffness Scores	
Control	0.89 ± 0.15	1.01 ± 0.27
FMS	0.83 ± 0.20	0.68 ± 0.14
FMS Plus	0.98 ± 0.08	0.78 ± 0.09
	Lack of Energy Scores	
Control	0.86 ± 0.16	1.07 ± 0.15
FMS	0.63 ± 0.10	0.51 ± 0.09
FMS Plus	0.92 ± 0.10	0.89 ± 0.10

TABLE 4 [continued]

Group	Three Months	Six Months
	Irritable Bowel Score	
Control	0.90 ± 0.21	1.06 ± 0.24
FMS	0.51 ± 0.11	0.48 ± 0.13
FMS Plus	1.23 ± 0.39	0.86 ± 0.10
	Average Symptoms Score	
Control	0.70 ± 0.11	1.01 ± 0.18
FMS	0.67 ± 0.06	0.56 ± 0.06
FMS Plus	0.99 ±0.06	0.90 ± 0.07
	Overall Health Scores	
Control	1.48 ± 0.41	1.15 ± 0.17
FMS	1.64 ± 0.25	1.93 ± 0.32
FMS Plus	2.04 ± 0.58	2.06 ± 0.77

* FMS = fibromyalgia syndrome

being very poor and 100 being exceptional. Thus, the direction of the scale was opposite from that of the symptoms scale. On average, subjects in the FMS group rated their overall health twice as good as it had been prior to the intervention program. Moreover, despite less of a noted impact on symptoms per se, the FMS Plus group reported almost a two-fold improvement in overall health. In contrast, control FMS subjects rated their overall health virtually the same as it had been at the start of the program [to 1.15 times that of their beginning score]. Thus, the overall improvement was substantial in both groups of FMS treatment group patients, as measured by self-report. These positive impressions were also conveyed by the verbal comments of most treatment subjects; many announced with regularity during and at the end of the program how much better they felt.

DISCUSSION

The hypothesis tested in the present study built upon and extended the work of Yunus (14), Moldofsky and Warsh (10), Russell et al. (9,11,12), Russell (21), Clauw (3) and others. We used a high specificity/sensitivity

LRA to identify immunoreactive substances [an array of substances commonly encountered by people in the course of daily life, covering common medications, foods and food preservatives, volatile organic chemicals, biocides, and other chemicals commonly found in the environment] which could chronically activate the immune system if repeatedly exposed to antigen above the neutralizing capacity of the phagocytic/dendritic "processing" system. After identification of immunoreactive substances, a comprehensive program of substitution of the identified reactive substances, and a diet and nutritive replacement program to facilitate structural and functional repair as well as enhance molecular and cellular detoxication competencies was instituted. Results of this approach led to substantial improvements in 11 of 13 persons with simple, uncomplicated primary FMS, and improvement in over half of the 12 with FMS Plus. In contrast, Cs who maintained their usual life-style over the six month periods exhibited minimal improvement [two of seven], further deterioration [three of seven] or no change [two of seven]. Interestingly, the improvements noted in this study are greater than improvements noted with other comprehensive programs, where often the degree of improvement is less, and fewer than 50% of patients show improvement (29-31).

Despite the considerable improvement noted, several concerns need to be acknowledged before a discussion of the study results can be offered. First, this study was neither blinded nor randomized; thus, it must be considered a quasi experimental design. Control subjects were not on any treatment program except for attending group support meetings. This may have instilled the perception that they were supposed to do worse. However, at the completion of the study, Cs were given an opportunity to follow the program and those that did [N = 3] have subsequently reported improvement in a post-study follow-up. Moreover, those in the T group may have improved by virtue of expectation effects on the subject of knowing that our intention to treat successfully was present. Unfortunately, these specific concerns cannot be evaluated within the design of this study. What is clear from this study, is that group support alone was not an effective treatment. If it were, one would have expected greater improvements in the C group.

Another limitation is that no clinical exams were conducted at completion for objective, clinical documentation of improvement; our study design relied completely on self-reported, identical questionnaires. However, given the magnitude of the changes reported subjectively, it is our expectation that clinical evaluations [if performed] would have confirmed patient-reported improvements.

Finally, the issue of participant compliance imposes another serious concern. We had a group leader who met with C and T subjects on a

regular basis at separate times to address concerns and issues with respect to the program and/or FMS *per se*. It became clear that not all subjects were following their dietary substitution and supplement programs fully, and that their discipline and commitment were not 100%. Self-reported compliance averaged 87% for the diet and 88% for the supplements; those with better compliance did improve to a greater extent. The prime requisites for this program to have its fullest expression are education, persistence, patience, commitment, and a willingness to change and go by results. Many people are unwilling to modify their life-styles. However, over a period of six months we would expect some subjects to forget to take their supplements, avoid the designated foods, etc., given holidays, vacations, and other events which promote relapses. Nonetheless, it may be that frequent contact with a skilled nutritionist or case manager could improve overall compliance. That possibility remains to be tested.

In the present study, numerous reactive substances [particularly haptenic] were identified in all FMS subjects. In particular, MSG was found to be reactive in 17 of 40 FMS patients. Other frequently reactive items included *Candida albicans*, caffeine, food coloring, chocolate, shrimp, dairy products [cow/bovine], and sulfites [see Table 3]. Typically, asymptomatic, healthy subjects have two or fewer positive responses out of 340+ items tested [unpublished data], whereas persons with autoimmune and immune dysfunction syndromes and conditions may present with 10 to 30 or more positive reactants [4 to 10% of all items tested]. While the number of positive responses noted by the LRA may seem high, when one examines the types of substances which evoked a positive response, it is far easier to explain. Most of the items are not actually foods, but rather food additives and chemicals to which most persons are exposed on a daily basis.

Although the questionnaire reports in the present study were variable over time, substitution of reactive substances by the T subjects resulted in marked differences as compared to Cs subjects. Hawley et al. (32) reported that FMS symptoms in individual patients are typically stable over time, but significant variability is commonly observed within subjects. We also noted marked inter–as well as intra-subject variation. Despite this variability, a steady improvement was noted for T but not for C subjects. The initial improvement noted for Cs at three months may reflect a placebo effect, or improvement due to the wish to be better. In contrast, neither of the experimental groups showed reversal of improvements at six months when compared to three month reports. However, because the T group reflected two cohorts [called primary FMS and FMS Plus in this report], the number of subjects in each experimental group was small enough that further studies are essential to confirm the statistical significance of this observation set.

The issue of competing/overlapping illnesses is of great interest. In particular, Buchwald and Garrity recently identified numerous clinical and demographic features of FMS, including age, gender, marital status, fatigue, sleep disturbances, arthralgias and others symptoms that were also shared by persons with chronic fatigue syndrome [CFS] and multiple chemical sensitivity [MCS] (33). This led Zeim to propose that people with FMS may in fact be misdiagnosed: they may have CFS or MCS rather than FMS (34). This possibility awaits further investigation, but is intriguing in light of the high frequency of environmental and chemical sensitivities noted in the present study. The diagnostic overlap between FMS, CFS, and MCS [and, perhaps reflex sympathetic dystrophy] awaits further clarification. Are these a common entity with various clinical expressions or are these distinct syndromes? It is also intriguing that women are more likely to be diagnosed with FMS whereas men are more likely to be diagnosed with CFS, MCS or a chronic myofascial sports injury disposition. Is it possible that there is a diagnosis bias for a common entity with multiple clinical manifestations but common causes in immune hyperstimulation of the neuroimmune control system? This study cannot answer, but does raise these questions.

In summary, we compared a novel program wherein immunoreactive substances were identified and then substituted in the diet and microenvironment of the patient. A reduction in total foreign reactive load was achieved; perfect avoidance was not the goal. After six months, many of the classic features of FMS had been ameliorated in patients on the T program, whereas in the C, usual life-style group of FMS subjects, no to minimal improvements were typically noted. This suggests that reducing the 'load' of immunoreactants below a threshold [which may be specific for the individual] in people with FMS may, as a consequence of re-establishment of resilience and homeostasis and the restoration of reserves in the neuroimmune control system, reset internal control mechanisms and allow for remission in cost effective ways. This may be particularly true in cases where current medical management can not yield controlled clinical trial results that improve upon results expected from placebo effects alone. Finally, outcome measures to document reduction of antigen exposure should be included in future studies.

REFERENCES

1. Felson DT: Epidemiologic research in fibromyalgia. J Rheumatol 16[supp19]: 7-11, 1989.

2. Waylonis GW and Heck W: Fibromyalgia syndrome: New associations. Am J Phys Med Rehab 71:343-348, 1992.

3. Clauw DJ: The pathogenesis of chronic pain and fatigue syndromes with special reference to fibromalgia. Med Hypotheses 44:369-378, 1995.

4. Wolfe F, Smythe HA, Yunus MB, Bennett RM, et al.: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 33:160-172, 1990.

5. Forseth KO and Gran JT: The prevalence of fibromyalgia among women aged 20 to 49 years in Arendal, Norway. Clin Rheumatol 21:74-78, 1992.

6. Wolfe F, Ross K, Anderson J, Russell IJ, and Hebert L: The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19-28, 1995.

7. Schochat T, Croft P, and Raspe H: The epidemiology of fibromyalgia. Br J Rheumatol 33:783-786, 1994.

8. Kravitz HM, Katz R, Kot E, Helmke N, and Fawcett J: Biochemical clues to a fibromyalgia-depression link: Imipramine binding in patients with fibromyalgia or depression and in healthy controls. J Rheumatol 19:1428-1432, 1992.

9. Russell IJ, Vipraio GA, Morgan WW, and Bowden CL: Is there a metabolic basis for the fibrositis syndrome? Am J Med 81[suppl 3A]:50-54, 1986.

10. Moldofsky H and Warsh JJ: Plasma tryptophan and musculoskeletal pain in non-articular rheumatism. Pain 5:65-71, 1978.

11. Russell IJ, Vaeroy H, Javors M, and Nyberg F: Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 35:550-556, 1992.

12. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, and Bowden CA: Platelet ^{3}H-Imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. J Rheumatol 19:104-109, 1992.

13. Russell IJ: Neurohormonal aspects of fibromyalgia syndrome. Rheum Dis Clin N Am 15:149-168, 1989.

14. Yunus MB: Towards a model of pathophysiology of fibromyalgia: Aberrant central pain mechanisms with peripheral modulation [editorial]. J Rheumatol 19:846-850, 1992.

15. Griep EN, Boersma JW, and de Kloet ER: Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. J Rheumatol 20:469-474, 1993.

16. Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, et al.: Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum 37:1583-1592, 1994.

17. Moldofsky H, Scarisbrick P, England R, and Smythe HM: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 37:341-351, 1975.

18. Bengtsson A and Henriksson KG: The muscle in fibromyalgia: a review of Swedish studies. J Rheumatol 16[suppl 19]:144-149, 1989.

19. Boissevain MD and McCain GA: Toward an integrated understanding of fibromyalgia syndrome. II. Psychological and phenomenological aspects. Pain 45:239-248, 1991.

20. Powers R: Fibromyalgia: An age-old malady begging for respect. J Gen Int Med 8:93-105, 1993.

21. Russell IJ: Neurohormonal aspects of fibromyalgia syndrome. Rheum Dis Clin N Am 15:149-168, 1989.

22. Caro XJ, Ojo-Maize EA, Agoplan MS, and Peter JB: Natural killer cell function in primary fibrositis (fibromyalgia) syndrome. Arthritis Rheum 36(9S): D114, 1993.

23. Hader N, Rimon D, Kinarty A, and Lahat N: Altered interleukin-2 secretion in patients with primary fibromyalgia syndrome. Arthritis Rheum 34:866-872, 1991.

24. Caro XJ: Immunofluorescent detection of IgG at the dermal-epidermal junction in patients with apparent primary fibrositis syndrome. Arthritis Rheum 27:1174-1179, 1984.

25. Simms RW, Felson DT, and Goldenberg DL: Development of preliminary criteria for response to treatment in fibromyalgia syndrome. J Rheumatol 18: 1558-1563, 1991.

26. Bryan W and Bryan M: Application of an *in vitro* cytotoxic reaction to clinical diagnosis of food allergy. Laryngoscope 70:810-924, 1960.

27. Pasula MJ: The ALCAT test: in vitro procedure for determining food sensitivities. Folia Med Cracov 34:153-157, 1993.

28. Jaffe R and Deykin D: Evidence for the structural requirement for the aggregation of platelets by collagen. J Clin Invest 53:875-883, 1974.

29. McCain GA, Bell DA, Mai FM, and Halliday PD: A controlled study of the effects of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia. Arthritis Rheum 31:1135-1141, 1988.

30. Kaplan KH, Goldenberg DL, and Galvin-Nadeau M: The impact of a meditation-based stress reduction program on fibromyalgia. Gen Hosp Psychiatry 15:284-289, 1993.

31. Wigers SH, Stiles TC, and Vogel PA: Effects of aerobic exercise versus stress management treatment in fibromyalgia: A 4.5 years prospective study. Scand J Rheumatol 25:77-86, 1996.

32. Hawley DJ, Wolfe F, and Cathey MA: Pain, functional disability, and psychological status: A 12 month study of severity in fibromyalgia. J Rheumatol 15:1551-1556, 1988.

33. Buchwald D and Garrity D: Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 154:2049-2053, 1994.

34. Zeim G: Chronic fatigue, fibromyalgia, and chemical sensitivity: Overlapping disorders. Arch Intern Med 155:1913, 1995.