Chapter 57

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The Role of Food Intolerance in Chronic Fatigue Syndrome

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Adverse reactions to foods can be a significant cause of symptoms in some patients with chronic fatigue syndrome, although the contribution of diet is not always easy to recognize. In order to understand why this is so, the problem of food intolerance must first be viewed in a broader perspective. For several decades, food "allergy" has been one of the most confused and controversial areas of clinical medicine. Only in recent years have advances in immunology, pharmacology and food science made it possible to begin understanding the diverse manifestations of food reactions and their underlying pathophysiology.[1,2] It is now becoming clear that although foods can have adverse effects for a variety of reasons, the vast majority of those encountered in clinical practice fall into two broad categories: food ***allergy,*** mediated by immunological mechanisms involving IgE antibodies, and non-immunological ***food intolerances,*** mediated by sensitivity to the pharmacological effects of various food substances.

Food Allergy

Allergies mostly occur in atopic individuals, Le. those who are genetically predisposed to make exaggerated IgE antibody responses against many environmental substances, inclu.ding, in some cases, certain food proteins. Clinically, food allergies exhibit a characteristic pattern.[3] They usually begin in infancy, against an atopic family background, and are

most commonly manifested by eczema and/or gastrointestinal symptoms. Typically, children react to just one or two specific foods, with eggs, milk, wheat, peanuts and fish, accounting for more than 90% of cases. Acute reactions can begin within minutes of ingestion with itching and urticaria around the mouth and lips, followed later by vomiting, abdominal cramps and diarrhoea, or an exacerbation of atopic eczema. Rarely, acute asthma, generalized urticaria or anaphylaxis can occur.

In acute cases the diagnosis is usually obvious from the history alone. If there is any doubt, testing for specific IgE by skin prick test or RAST can be performed. A strongly positive result may strengthen a clinical suspicion, but it must be borne in mind that atopic individuals often have IgE antibodies to foods which cause them no clinical symptoms whatsoever. A negative test result therefore has more diagnostic significance than a positive one. In children with chronic symptoms the most reliable means of diagnosis is to withdraw the suspected foods for several days or weeks, allow the symptoms to subside, and then cautiously reintroduce foods one-by-one as oral challenges under close supervision.

The mainstay of treatment is avoidance. Most children "grow out" of their food allergies before puberty, particularly those involving eggs, milk or wheat. Cautious challenges can be carried out every 6 to 12 months, and once symptoms no longer occur the food can be gradually reintroduced into the child's diet. Allergies to peanut and fish are more likely to be severe and persistent, so that lifelong avoidance may be necessary.

Food Intolerance

The symptoms provoked by non-immunological food reactions are more varied and fluctuating than those caused by food allergy.4 Although in some cases reactions are clinically clear-cut, in others they can be vague or non-specific, and their cause is often obscure. When a relationship between symptoms and diet is recognized, many foods may be suspected, but the variability of responses can be misleading. The reason for this is that reactions are caused by a variety of chemical substances, each common to many foods, and symptoms fluctuate according to the cumulative doses ingested.

Food chemicals

Although much attention has been paid in recent years to the adverse effects of food additives, naturally occurring food chemicals are a more insidious and more common cause of problems. Natural chemicals play a central role in the complex symbiotic relationship between animals and plants which has developed as a result of co-evolution.[5] Plants are known to be capable of synthesizing an enormous range of substances important for their own survival and reproduction. Amongst these are a variety of anti-microbial and anti-parasitic agents, as well as chemicals which can modify the feeding behaviour of insects and higher animals. Not surprisingly, some of these substances can be toxic to humans if ingested in significant quantities.

For their part, higher animals have developed elaborate sensory, metabolic and excretory mechanisms for the avoidance, detoxification and elimination, respectively, of potentially toxic plant chemicals. In addition, through agriculture and selective breeding over thousands of years, the human diet has evolved in such a way as to avoid the more dangerous of these substances. Of course, not all natural chemicals are harmful, at least in the amounts normally consumed. Indeed, some are essential nutrients (vitamins). Others are responsible for the distinctive flavours, aromas and psychophysiological effects which make many foods and drinks so pleasurable. Still others have been exploited for their medicinal properties. In many cases, however, adverse effects can become apparent when higher than usual doses are ingested. Furthermore, within any population there is a distribution of individual responsiveness to such substances. Thus, many commonly eaten foods, especially those derived from plants, contain chemicals which, though of generally low toxicity, can nevertheless have significant adverse effects in susceptible individuals.

Adverse reactions

The most carefully studied natural chemicals known to be capable of provoking adverse reactions are salicylates, biogenic amines, and glutamate. In general, the strength of flavour and aroma of foods is a good guide to the concentration of these substances.

Salicylates, along with many other benzoic acid derivatives, are found in varying concentrations in most fruits and vegetables, nuts, herbs and spices, jams, honey, tea, coffee, wines and many other plant-derived foods and drinks.6 We have estimated that an average Western diet may contain between 10 and 100 milligrams per day of natural salicylates alone.

Biogenic amines are present in chocolate, cheese, fish products, aged or processed meats, bananas, oranges, avocados, tomatoes, wines and beer, amongst other foods.[7]

Free glutamate (i.e. non-protein-bound) is present naturally in many strongly flavoured foods such as tomatoes, mushrooms, tasty cheeses, gravies, sauces, stock cubes, meat extracts and yeast extracts;8 its purified sodium salt (MSG) is also used as a flavour enhancer and has achieved notoriety for causing the "Chinese Restaurant" syndrome.

From this brief description it will be clear that not only is each substance found in many foods, but also that a given food may contain several offending chemicals. To further complicate the picture, intolerances are highly idiosyncratic, both in relation to the provoking agents and the symptoms provoked. Affected individuals are frequently sensitive to several substances, including both natural food chemicals and additives, the particular symptoms provoked depending on target organ susceptibility.4

The underlying causes of most food intolerances are unknown, but clinical observations suggest that they are likely to have a pharmacological basis. Reactions are dose-dependent, and it is common to observe withdrawal effects, tachyphylaxis and supersensitivity when intake is modified. The range of symptoms is very similar to those seen as a result of drug side-effects and, indeed, it is common for food-sensitive patients to react adversely to various drugs as well. Not surprisingly, there appears to be a genetic predisposition. A positive family history is very common, and there is a tendency for specific sensitivities to cluster within affected families. In addition, women are affected two to three times more frequently than men, and can sometimes date the onset of symptoms to menarche, pregnancy or the taking of oral contraceptives, suggesting that hormonal factors may play a part.

Table!

Clinical manifestations of food intolerance

Major syndromes *	Associated symptoms *
urticaria/angioedema	mouth ulceration
migraine	vaginal, bladder irritation
irritable bowel	nasal & sinus congestion
	irritability, depression
	'hyperactive' behaviour
	constitutional symptoms (fatigue, malaise, myalgia, headache, etc)

* Subdivisions refer to the most common presentations. However, in *some* cases symptoms listed in the 'associated' column may be the dominant clinical problem.

Clinical manifestations

The most common clinical manifestations of food intolerance are listed in Table 1. Reactions can begin at any age, the peak incidence being in the third and fourth decades. Symptoms often begin insidiously, but about one third of patients date the onset to a severe viral infection or other illness, an adverse drug reaction, a sudden change of diet, or some combination of these events. Chronic or recurrent urticaria and angioedema, irritable bowel syndrome (IBS), or migraine may be isolated presenting syndromes, or may occur in association with one or more of the other symptoms listed. In some cases, constitutional symptoms such as malaise, fatigue, headache, and flu-like aches and pains can dominate the clinical picture, occasionally leading patients to the mistaken belief that they are harbouring a "chronic virus infection" if food intolerance is unrecognized. In children, recurrent headaches, abdominal and limb pains are not uncommon, and may be associated with lassitude, irritability or 'hyperactive' behaviour.

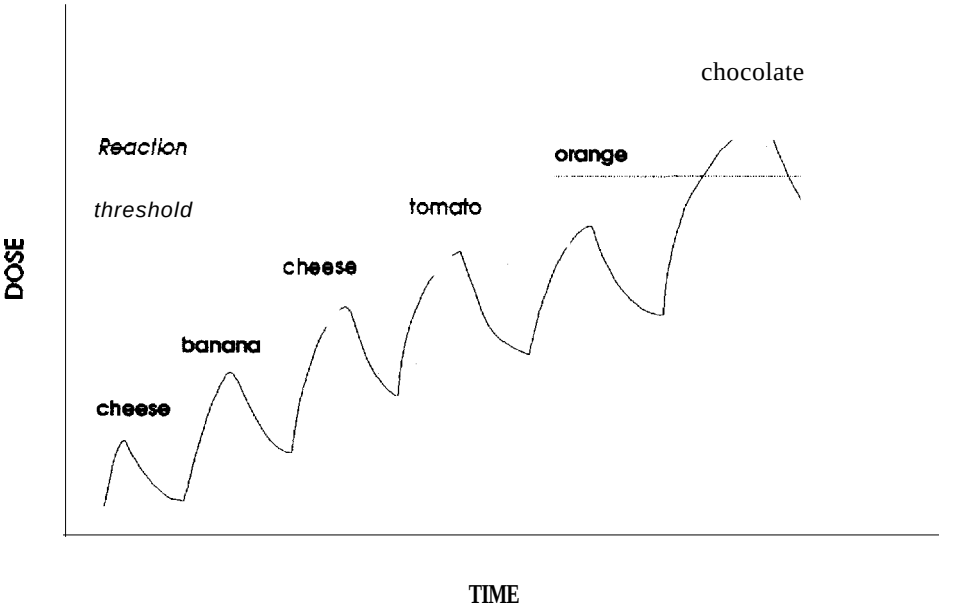
In atopic patients the picture can be complex, since allergies and intolerances sometimes co-exist. In our experience, about one third of food-sensitive children with eczema have a clinically significant food allergy, whereas over 90% have demonstrable chemical intolerances. Food-sensitive asthmatics commonly react to sulphite preservatives, less often to salicylates and/or glutamate, and rarely to true food allergens.

Patient evaluation

In patients presenting with known or suspected food reactions, initial assessment should be aimed at determining whether symptoms are likely to be due to an allergy or to chemical intolerances, since this will determine subsequent investigation and management. Four aspects of the history are particularly important: (i) age of onset, (ii) a personal or family history of atopy, (iii) the pattern and nature of symptoms thought to be provoked by foods, and (iv) the specific foods known or suspected to be involved. Psychological aversions to specific foods can sometimes complicate the picture, but can usually be distinguished with a careful history and systematic testing.

Figure!

Cumulative effects of food chemicals



A variety of foods which share a common chemical component, eaten over several days, can contribute to the development of symptoms once the cumulative dose has exceeded the individual's reaction threshold. In this example, cheese, bananas, tomatoes, oranges and chocolate all contain biogenic amines, but the patient is likely only to incriminate the chocolate. On a different occasion, however, the same amount of chocolate in the absence of these other contributing foods may not reach threshold levels and might not provoke any symptoms.

Food reactions in children may be due to allergy, intolerances, or both, but those which first begin in adolescence or adult life can be assumed to be intolerances until proven otherwise. Similarly, symptoms such as recurrent urticaria, angioedema and mouth ulceration have a high probability of being due to food intolerance, even though the patient may be unaware of a relationship with diet. On the other hand, headaches, irritable bowel and most of the other associated symptoms listed in Table 1 are less specific. Even when food intolerance is known to be involved, it may be only one of several factors, both physical and emotional, capable of triggering the same symptoms in a susceptible individual. In these circumstances dietary investigation can be a very useful tool since these other factors are much easier to evaluate once the dietary variables have been eliminated.

The diet history is the least reliable. Whilst it is often possible to identify a food allergy from the history alone, intolerances are much more difficult to pinpoint in this way. Unlike allergies, reactions to food chemicals are typically delayed, usually by some hours, but by as much as a day or two in some cases. Acute reactions from a particular food can occur if the individual's dose threshold is exceeded, but this depends on what other foods have been eaten over the previous few days (Figure 1). More often, chronic or recurrent symptoms are provoked by the cumulative effects of several chemicals present in many different foods in the daily diet. Thus, it is not surprising that only about 50% of patients are aware of any connection at all between diet and their symptoms, and that fewer still are able to accurately identify the specific foods involved.

Clinically obvious reactions are most likely to occur with foods containing high concentrations and/or combinations of the relevant chemicals (e.g. highly flavoured or spicy foods, processed foods, confectionery, wines, etc.) and the experienced practitioner may then be able to make an educated guess about which substances are likely to be responsible. How-

ever, in most cases a definitive diagnosis cannot be made without systematic dietary testing. In general, patients who present with a belief that their symptoms are diet-related usually prove to be correct, but they can easily reach the wrong conclusions about which specific foods are involved.

Investigation and management

In the absence of any suitable diagnostic tests for food intolerance, the only reliable method of investigation is by elimination and challenge testing. The principle behind this approach is first to remove all the suspected foods and food substances from the patient's daily diet and then, if and when symptoms subside, to reintroduce them one by one as "challenges", preferably administered double-blind.

The details of this approach vary considerably between different centres. Within Australia most teaching hospitals have now adopted procedures based on the elimination diet and challenge protocols developed at Royal Prince Alfred Hospital over the past decade. Patients are placed on a stringent diet free of natural salicylates, amines, glutamate and food additives for a period of two to six weeks, depending on clinical response. Milk, wheat, and/or eggs may also be eliminated, depending on the circumstances, and can be reintroduced later as open challenges. Patients whose symptoms subside are given a battery of chemical challenge capsules containing graded doses of purified food substances and placebos, administered in a random order at 48-hour intervals. Symptoms are recorded in a diary, and once the challenges are completed the code is broken for each patient and the results interpreted. In most cases, investigation can be carried out on an outpatient basis, but if there is a history of anaphylactoid reactions, laryngeal oedema or moderate to severe asthma, challenges are performed under careful supervision in hospital. In our hands, symptomatic improvement with dietary elimination occurs in approximately two-thirds of patients with recurrent urticaria, and 40-50% of those presenting with headaches or irritable bowel syndrome. To illustrate the usual reaction pattern, results of challenge tests in these groups are shown in Table 2.

Once the substances responsible for provoking symptoms have been identified in each case, an individually tailored diet can be prescribed for long-term management. Total abstinence is rarely necessary. After 4-6 weeks of strict adherence, patients are instructed to begin gradual dietary liberalization to determine their individual reaction threshold with foods grouped according to chemical content. Often, regular ingestion of small amounts leads to an increase in tolerance over a period of weeks or months, and some patients may eventually be able to return to a relatively normal diet. In other cases, symptoms can recur insidiously, indicating a need for more stringent avoidance.

Successful dietary management requires the involvement of an experienced dietitian. Attention to seemingly minor details is crucial, and compliance is enhanced greatly by the provision of practical advice about shopping, preparation of meals, social occasions, etc., as well as telephone access to clarify uncertainties as they arise.

Table 2

Double-blind challenge responses (%)*

Challenges	Presentation: Urticaria	Migraine	LB.S.
Active:			
salicylates	61	51	62
amines	29	52	39
glutamate (MSG)	33	54	48
preservatives	47	51	39
antioxidants	29	33	38
propionate	19	32	37
nitrates	38	58	47
tartrazine	34	43	36
erythrosine	35	31	40
brewers yeast	30	40	32
gluten	2	7	16
lactose	7	11	18
placebos:			
starch	5	8	8
sucrose	2	7	5

* Response rates refer only to provocation of main presenting symptoms. Various other symptoms were provoked by each challenge in an additional 0-14% of cases. Numbers of patients challenged in each group were: urticaria 614; migraine 109; irritable bowel 159.

DIET AND CHRONIC FATIGUE SYNDROME

As outlined above, in some patients with food intolerance, constitutional symptoms can dominate the clinical picture, or can be the sole manifestations. They include fatigue, headache, musculo-skeletal aches and pains, malaise, and a variety of neuropsychiatric symptoms such as irritability, depression, impaired memory and concentration, sensory and visual disturbances. Indeed, patients may present with a clinical picture typical of "chronic fatigue syndrome".9 It should be stressed, however, that the clinical spectrum of food intolerance is such that individual patients can experience any combination of symptoms, with varying degrees of severity, so that precise categorization can be somewhat arbitrary at times.

Challenge test results

We have investigated a total of 966 patients presenting with constitutional symptoms at Royal Prince Alfred Hospital over a nine year period (Table 3), representing about 20% of all patients referred to our clinic for dietary evaluation. Of the 966, approximately one third would satisfy criteria for the diagnosis of chronic fatigue syndrome, although as implied above, the dividing line is not always clear. Ages ranged from 5 to 85 years, with more than 50% falling between 20 and 45 years, and females outnumbered males by 3:1. All patients were initially offered a strict elimination diet to screen for possible food intolerance. Overall, 656 patients reported subjective improvement, and of these 497 underwent formal double-blind, placebo-controlled challenge testing. The remaining 159 were prescribed an empirically modified diet based on open food challenges.

Table 3

Patients presenting for dietary testing: constitutional symptoms

	No. of patients
Challenged	497
Empirical diet	159
In progress	34
No improvement	79
Lost to follow-up	197
Total	966

The proportion of patients reacting to each of the double-blind chemical challenges is shown in Table 4. Several points are worthy of note. To begin with, the hierarchy of responses is very similar to that seen in other patient groups presenting with recurrent urticaria, migraine and irritable bowel syndrome (Table 2). Salicylates were the single most common challenge to provoke reactions, followed by preservatives, glutamate, amines and the various other food additives. Brewers yeast contains a complex mixture of phenolic substances, and is most likely to provoke reactions in patients who are sensitive to both salicylates and amines. Gluten and lactose reactions were the least common, and when they did occur there was a tendency for them to provoke mainly gastrointestinal symptoms. The overall placebo reaction rate was low, at around 10%, a result we attribute to the reduction of "background noise" by maintenance of stringent dietary restriction throughout the challenge period.

It is noteworthy that each challenge is capable of provoking any or all of the symptoms, the pattern being highly idiosyncratic but reproducible in each individual. Moreover, by adding the percentages in each column it will be clear that most individuals reacted to several different challenges, the mean being around six, and that each substance was capable of eliciting several symptoms. Overall, it has been our clinical observation that of all patients with food intolerance, those with fatigue and other constitutional symptoms are the most sensitive, reacting to a broader range of challenge substances, with lower dose thresholds and more prolonged symptoms.

Clinical outcome

The long-term benefits of dietary modification in patients with chronic fatigue syndrome are more subjective and difficult to quantify. Nevertheless, we have recently conducted a retrospective survey (follow-up period 12 months to 8 years) in an attempt to gain some insight into this question. Altogether, 225 contactable patients who satisfied our criteria for a diagnosis of chronic fatigue syndrome, were sent a questionnaire by mail. Of these, 153 had undergone dietary investigation. At the time of writing, 102 replies had been received. Patients were first asked to give a global, qualitative assessment of their response to the elimination diet during initial testing

Table 4

Symptoms (%) provoked by challenges (495 patients)

CHALLENGES	Total Reactions (%)	fatigue	aches & pains	CNS& mood	headache	G.!. Tract
Salicylate	75	24	16	27	33	41
Amines	65	23	13	17	33	27
Glutamate (MSG)	66	24	14	21	33	32
Preservatives	67	23	13	21	32	32
Antioxidants	55	19	11	17	24	25
Nitrates	64	20	13	16	33	33
Propionate	53	17	9	16	22	29
Tartrazine	57	20	12	18	27	24
Brewers yeast	46	17	11	13	23	20
Gluten	22	9	5	6	9	11
Lactose	23	8	4	5	11	13
Starch (placebo)	12	5	3	4	6	5
Sucrose (placebo)	9	3	2	3	5	4

(Table 5). A little over one third of the respondents considered themselves to have been "much better" or "completely well", whilst nearly two thirds recalled having felt "no better at all" or only "a little better".

Table 5

Symptomatic response to elimination diet

Global response	No. of patients
"No better at all"	, 38
"A little better"	25
"Much better"	32
"Completely well"	7
TOTAL	102

Patients were next asked whether they were still restricting their diet at the time of follow up, and if so, to what degree. The responses are shown in Table 6. Not unexpectedly, those who initially felt "much better" or "completely well" had continued to restrict their diet, in most cases stringently. Interestingly, however, more than half of those who recalled feeling "no better at all" on the initial elimination diet had also continued with significant long-term restriction.

Table 6

Maintenance of long-term dietary restriction

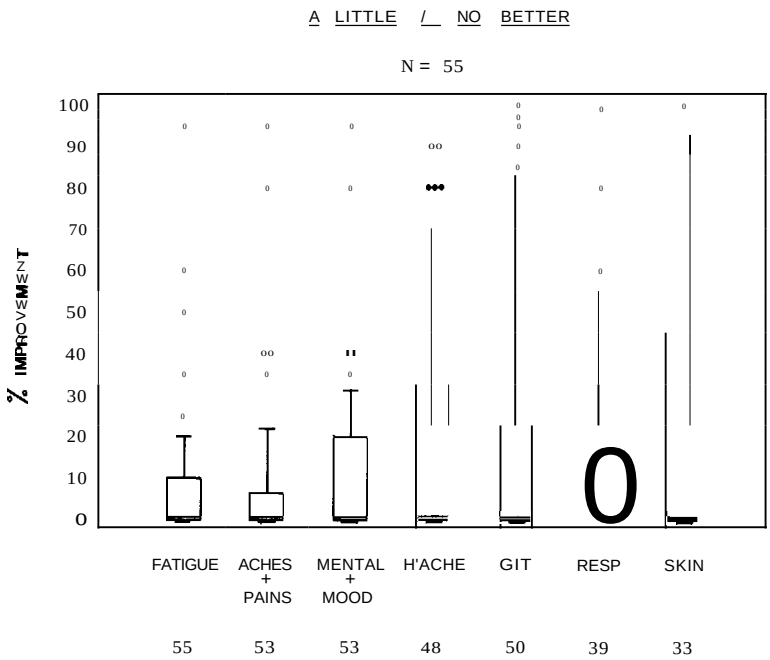
Initial response	Degree of restriction	
	Any degree	Moderate / severe
'No better'	65%	51%
'A little better'	88%	71%
'Much better'	100%	84%
'Completely well'	100%	83%

At first sight this is a puzzling result. However, our clinical experience has been that even though a patient's global state may not be significantly improved, specific symptoms can respond to dietary

modification, sometimes dramatically, with recurrence when the offending substances are reintroduced. The converse is also true, in that patients whose global state is significantly improved may nevertheless find that certain symptoms persist, regardless of the extent to which their diet is restricted.

These clinical impressions were confirmed by responses to the follow-up questionnaire. Patients were asked to subjectively rate the percent improvement in each of their major symptoms as a result of long-term dietary restriction. The results amongst those who had originally considered themselves "much better" or "completely well" on the test diet are summarized in Figure 2. On average, all symptoms remained substantially reduced in this group, headaches showing the most consistent benefit overall. More detailed analysis of responses, however, showed significant individual variability, with no reproducible pattern. Not surprisingly, patients who felt little or no better on the initial elimination diet reported little or no long-term improvement either, on average (Figure 3).

Figure 3



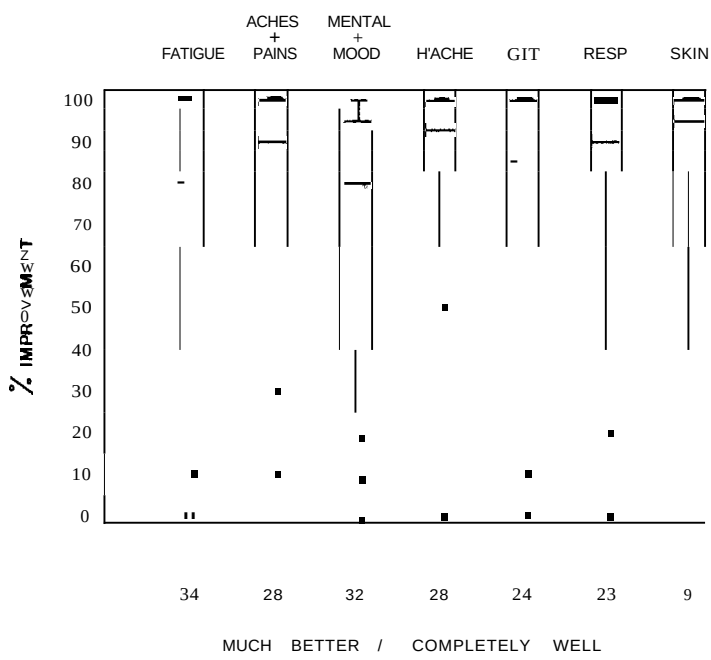
Figures 2 & 3 *Boxes show 25th, 50th and 75th percentiles; bars indicate 90th percentiles; closed circles are remaining outliers.*

Nevertheless, individual patients did sometimes obtain significant relief from specific symptoms, most notably headaches, gastrointestinal and skin reactions.

Selection of patients for dietary investigation

Clearly, not all patients with chronic fatigue can or should undergo the kind of time-consuming dietary investigation outlined above. The elimination diet itself is demanding, inconvenient, socially restrictive and, above all, boring. On top of this the challenges are intended to provoke symptoms which may be distressing and usually continue for several hours or days (even two or three weeks in rare cases). The whole process usually takes between two and three months, and although some patients benefit, many do not. On the other hand, when patients do benefit they can sometimes obtain dramatic relief of long-standing, debilitating symptoms. Even when improvement is less dramatic it can lead to a significant improvement in quality of life and return to productivity for the

Figure 2



chronically ill. In such cases, even a major change of diet may be considered a small price to pay.

Is dietary investigation warranted?

How, then, can the doctor and patient decide whether dietary investigation is warranted? The main factors to be weighed are: the severity of the symptoms, the motivation of the patient, and the probability of success. Severity is very subjective, but can be judged to some extent according to how badly the individual's daily life is disrupted, including work, family life, leisure and recreation. Motivation depends not only on the patient's degree of distress and desire to improve, but also on attitude to food and willingness to sustain the necessary inconveniences during testing.

Before making a final decision, most patients ask about the probability of success. The true prevalence of food intolerance in chronic fatigue syndrome is difficult to determine with confidence. Our estimate is that it is a significant factor in 20-30%, and may be the principal trigger in perhaps 5-10%, though we hasten to add that these figures are subject to an unquantifiable selection bias.

Clinical Clues

There are several clues in the history which may increase the clinician's index of suspicion that food intolerance is a factor: (a) recurrent urticaria, angioedema, and/or mouth ulceration (past or present); (b) associated gastrointestinal symptoms and/or migraine; (c) known food reactions; (d) aspirin or other drug intolerances; (e) a strong family history of food intolerance.

Overview

It is evident from the above observations that the relationship between food intolerance and chronic fatigue syndrome is a complex one. Thus, within the clinical spectrum of food intolerance, we find that pathological fatigue, in varying degrees of severity, is a common symptom. At one end of this spectrum is a sub-group of patients with typical chronic fatigue syndrome, with or without other food-associated symptoms. Conversely, looking from the perspective of patients presenting with chronic fatigue syndrome, we find that food intolerance can assume varying degrees of significance. In some cases, food plays no discernible part whatsoever in triggering symptoms, whilst in others, symptoms can resolve completely when the diet is suitably modified, with all grades in-between.

The role of viruses is also complex. In agreement with other reports, 35% of patients presenting to our clinic with chronic fatigue syndrome had a clinically evident acute viral infection at the onset of their illness. Two thirds of these were documented EBV infections, but a number of other organisms were implicated in specific cases e.g. influenza, hepatitis B, varicella, rubella, herpes simplex. Enteric infections acquired whilst travelling appeared to be the trigger in several patients, though the responsible organisms were rarely identified. Interestingly, there was no difference in the incidence or distribution of infections between those who proved to have significant food intolerance and those who did not. It is relevant to note that a careful history will implicate a viral infection at the onset of the disorder in some 20 to 30% of all patients with food intolerance, regardless of the clinical manifestations. Thus, chronic fatigue syndrome should not be regarded as unique from this point of view.

It should also be emphasized that infection itself may not always be directly to blame for triggering symptoms. Careful questioning often reveals concurrent events whose significance may only become apparent in retrospect, after dietary testing. For example, many of our patients who suffered an acute viral illness at the outset stopped eating regular meals, consuming instead large amounts of preserved soft drinks, citrus fruit, tea, soups, broths etc. At the same time they often took various medications such as aspirin or other anti-inflammatory and analgesic preparations, proprietary cold and 'flu remedies, cough suppressants, coloured and flavoured lozenges or syrups, antihistamines, sympathomimetics and/or antibiotics. In patients with a sensitive constitution this combination of dietary and pharmaceutical stimuli can be a major insult, particularly when coming on top of an acute systemic inflammatory reaction. Once established, overt food intolerance can then become a self-perpetuating problem, pro-

ducing recurrent flu-like symptoms which are easily mistaken for a "chronic virus infection".

PATHOGENESIS

Clinically, there are several striking features of chronic fatigue syndrome: the severity of the symptoms compared with the paucity of physical signs; the absence of significant immunopathology; the fluctuating course (short-term and long-term); the occurrence of spontaneous remissions (occasionally full recovery) even after prolonged illness; and the lack of long-term progression in most cases. **In** particular, patients do not exhibit persistent fever, lymphadenopathy, splenomegaly, leukocytosis, or other signs of a chronic inflammatory process. Indeed, persistent changes in acute phase reactants, serological abnormalities, or evidence of tissue pathology are so rare that, when evident, they suggest the presence of some other undiagnosed disease. Since, in general, the symptoms of viral infections are mostly attributable to the host response, these features themselves, do not support the theory that chronic fatigue syndrome is due to a "chronic active" viral infection.

Immune competence is also typically normal in patients with chronic fatigue syndrome, as judged by their ability to clear intercurrent infections efficiently, and by the absence of repeated or progressive infections with specific organisms, opportunistic or otherwise. Although we do not routinely test immunological function in our own patients, we have done so in selected cases and generally find the results to be within the normal range. **In** our view, the findings reported by others are non-specific and likely to be of a secondary nature.

Hypothesis

On the basis of the above arguments, the evidence that chronic fatigue syndrome is caused by a chronic viral infection or a primary immunological disorder seems unconvincing, pointing to the need for a fresh approach in attempting to understand this puzzling condition. Similarly, the mechanisms of most adverse food reactions are poorly understood, with no satisfactory explanation for their diverse clinical manifestations. The relationship described here between food intolerance and chronic fatigue syndrome thus provides us with an opportunity to formulate a unifying hypotheses by which to try and comprehend both problems.

> We propose that both food intolerances and chronic fatigue syndrome are manifestations of primary (perhaps heterogeneous) disorders of neuroregulation, involving abnormalities in the function of one or more receptor families which regulate synaptic transmission.

This hypothesis is based on two separate lines of evidence. The first derives from the clinical associations described here between migraine, irritable bowel syndrome, recurrent urticaria and chronic fatigue syndrome. **In** each case, an argument can be made that neuroregulatory mechanisms are involved in pathogenesis. The second line of evidence arises from the observation that food intolerance can trigger symptoms in each of these apparently diverse conditions, suggesting that there may be common mechanisms linking them. Considering the nature of the chemical triggers in such patients, and their response characteristics, it is likely that receptor-mediated abnormalities of synaptic transmission and! or neuromodulation are involved.

Clinical associations

Migraine and irritable bowel syndrome are relatively easy to comprehend as neurogenic disorders. **In** migraine, premonitory and prodromal symptoms preceding headache point clearly to central nervous system (CNS) involvement, although whether this reflects a primary neurogenic event or is secondary to vascular changes remains a subject of debate. Over the past three decades much interest has focused on abnormalities of serotonin release as the basis of the vascular changes in migraine.[12,13] Pain is thought to be mediated by perivascular nerve fibres which contain the sensory neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) along with vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY),[14] and both SP and CGRP have been shown to be released during headache.[15,16] Although it is generally agreed that these mechanisms are activated in migraine, attention has increasingly shifted towards possible primary CNS abnormalities. Evidence is accumulating that a phenomenon analogous to the spreading depression of Leao[17] may

be involved, and it has been suggested that this may be mediated by abnormalities of excitatory (glutamate) or inhibitory (gamma aminobutyric acid, GABA) neurotransmitter function.[18] There has also been considerable interest in the central serotoninergic system, but its pathophysiological role remains to be determined.[19]

Irritable bowel syndrome is characterized by abnormalities in motility of the small and large intestine and abnormal responsiveness to various neurohumoral stimuli,[20] consistent with an abnormality of neuroregulation.[21] In recent years it has become evident that the enteric nervous system is comparable to the spinal cord in terms of the number of neurons present and their structural and neurochemical complexity.[22] In addition to classical neurotransmitters, enteric neurons produce at least 14 neuropeptides, including VIP, SP, NPY, CGRP, cholecystokinin (CCK), enkephalin, dynorphin, and peptide histidine-isoleucine (PHI).[22] Furthermore, peptides released in the CNS have been shown to influence gastrointestinal motility, including CCK, NPY, SP, thyrotropin-releasing hormone (TRH), corticotropin-releasing factor (CRF), neurotensin, oxytocin and somatostatin.[23] Although specific abnormalities have not yet been identified, it is interesting to note that increased irritability has also been found in other organs in patients with irritable bowel syndrome.[24,25,26]

In recurrent urticaria and angioedema the role of neural mechanisms is at first sight more difficult to discern. Drugs, chemicals, foods and physical stimuli are generally believed to release histamine and other mediators from mast cells by pathways not involving IgE, but precise mechanisms have not been delineated in most cases.[27,28] However, there are some tantalizing clinical clues which suggest that neurogenic pathways are involved: the anatomical distribution of lesions; the occurrence of a localized sensory prodrome in some patients; and the common tendency for pressure and other physical stimuli to trigger lesions. It is interesting to note, therefore, that in normal human skin peptides such as SP, VIP, somatostatin, neurotensin, and certain endorphins are capable of stimulating mast cell degranulation.[29] "Neurogenic inflammation" and the axon reflex are thought to be mediated by the release of SP from sensory C-type fibres in the skin, causing release of histamine from nearby mast cells.[30-33] Recently, peptidergic nerve fibres have been observed making direct contact with mast cells in various tissues, providing a structural basis for this interaction.[34-36] Taken together, this evidence has led us[4] and others[37,38] to speculate that recurrent "idiopathic" urticaria and its physical variants might involve an abnormality in the neural regulation of mast cell function.

> Thus, we would argue that the common thread linking migraine, irritable bowel syndrome and recurrent urticaria in patients with food intolerance is an abnormality of neuroregulation.

From here, it does not take a large leap of imagination to suppose that chronic fatigue syndrome might also have a similar basis. Involvement of the CNS would explain many of the bizarre neurological and psychological manifestations of the condition, and could also account for the gastrointestinal and other autonomic symptoms which can be prominent in some patients. Furthermore, it then becomes easy to comprehend the increased sensitivity of such patients to diverse pharmacological stimuli (drugs, alcohol, food chemicals, smells and fumes) and to endogenous factors (stress, exercise, hormonal changes). Finally, on this view, viruses would be seen as triggering clinical symptoms via the exaggerated central effects of inflammatory mediators and lymphokines.[39,40]

Chemical stimuli

The next question is, can we be more specific in considering the nature of such putative neuroregulatory abnormalities? To examine this, we turn to the various stimuli capable of triggering symptoms in different individuals, in particular, the food chemicals described above. The first point to note is that reactions to these substances are highly specific in each individual, even amongst chemicals which are closely related structurally such as the various benzoic acid derivatives, with no predictable pattern. Once established, idiosyncrasies remain fixed over time even though the reaction threshold can vary. Secondly, reactions to these substances exhibit dose-dependence, tachyphylaxis, tolerance, withdrawal reactions, and supersensitivity with chronic ingestion or after abstinence. These phenomena, taken together, are highly characteristic of receptor mediated alterations in synaptic transmission.[41]

The specificities of such receptors, and their possible locations are open to speculation. However, the enormous complexity of neuroregulatory mechanisms now emerging[42,43] should caution us against oversimplification. In addition to the "classical" neurotransmitters there are now over 40 known peptide and other neurotransmitters, each with their own family of receptors, and the number is still growing. Co-localization of several transmitters in a single neuron has become the rule rather than the exception, with some cells containing as many as five. Almost any combination is possible. They can be released together or separately, and their physiological effects can be enormously varied depending on the target cell types and receptors expressed.[42] One interesting feature of neuropeptides is the distinction between their direct actions as effectors of neurotransmission, and their indirect actions in modulating the actions of other transmitters.[43] These are independent properties mediated by different mechanisms. Both can be highly specific (implying action through receptors or other binding sites), but neuromodulation is characterized by slow onset and long duration, slow desensitization, and in some cases multiple actions contributing to a coordinated physiological or behavioural effect.43

What inferences can we make, then, from a closer examination of adverse food reactions? One likelihood is that food chemicals act by altering neuromodulation rather than direct neurotransmission, since reactions are typically delayed in onset, and can last for hours or days. Another is that they can probably act through a multiplicity of receptor subtypes, given the structural diversity of the substances involved, and their protean clinical manifestations. However, the fact that several apparently unrelated substances can cause the same set of symptoms in a given individual suggests that there may be convergence of different pathways onto particular target cells and/or 'cross-talk' amongst the different receptors involved.44 This is supported by our clinical observation of cross-desensitization and cross-tolerance between different substances to which a given individual may be sensitive.

Regarding the actions of specific food chemicals, it is plausible (but perhaps too simplistic) to imagine, for example, that foods containing biogenic amines might act via one or more monoamine receptors. Similarly, the fact that glutamate is physiologically an excitatory neurotransmitter makes it tempting to speculate that abnormally functioning endogenous receptors might be at fault in MSG-sensitive patients.[45] Although there are now well established examples of 'excitotoxic' amino acids causing neuropsychiatric disorders via NMDA receptors,46 it should be borne in mind that such cases involve neuronal cell death and irreversible structural pathology, unlike the conditions we are considering here.

Since salicylates are the most common of our challenge substances to elicit reactions, it is of considerable interest to examine their possible mechanism of action. There are four main hypotheses to explain aspirin idiosyncrasy as a cause of urticaria and/or asthma:

(1) cyclooxygenase blockade with diversion of arachidonate into the lipoxygenase pathway,

(2) "direct" mast cell degranulation,

(3) activation of the complement cascade,

(4) activation of the contact system with excess kinin formation.[47]

Of these, the first is the most widely accepted,48 but detailed review of the evidence has led to the conclusion that the true mechanisms remain unknown.[49] Our own finding of cross-sensitivity between sodium salicylate, acetylsalicylic acid, sodium benzoate, 40H-benzoate and amines, as well as structurally unrelated compounds such as metabisulphite, tartrazine and MSG, also argues strongly against a primary disturbance of arachidonic acid metabolism. What of other known actions of salicylates such as uncoupling of oxidative phosphorylation or free radical scavenging?50 At present there is no clinical or laboratory evidence to implicate them, and the cross-sensitivities above argue against the possibility. More informative, perhaps, are the well-known clinical manifestations of chronic salicylate intoxication: headache, nausea, vomiting, diarrhoea, blurred vision, tinnitus, vertigo, and CNS symptoms such as lassitude, drowsiness, confusion, restlessness, excitement, tremor, progressing in severe cases to hallucinations, delirium, convulsions, and eventually coma. Although some of these toxic effects may be secondary to metabolic changes, many of the eNS

manifestations are thought to be due to the direct effects of salicylates on neuronal function. The latter include alterations in GABA and serotonin production, altered membrane permeability and reduced synaptic transmission.[50]

Finally, given the clinical evidence of a strong familial predisposition to the various clinical disorders associated with food intolerance, the question arises as to what might be the molecular and genetic basis of the proposed neuroregulatory abnormalities discussed above.

A possibility we find particularly attractive is that there may be allelic heterogeneity within the population at receptor gene loci.

Although such polymorphisms have not yet been demonstrated in receptor molecules, there is ample biological precedent for this suggestion. Thus, if minor variations in amino acid sequence were located near a transmitter binding site, allosteric sites or other conformationally sensitive parts of the molecule, it would be easy to envisage subtle changes in molecular function. This could include altered affinity for endogenous and exogenous agonists and/or antagonists, changes in receptor turnover and numbers, or alterations in signal transduction mechanisms. Functionally significant allelic variation could also occur in ion channels linked to receptors, or in one or more of the growing family of regulatory G proteins.[51]

We do not consider these various possibilities to be mutually exclusive; indeed, clinical expression of chemical idiosyncrasies might well require the presence of more than one such abnormality. Moreover, even if our speculations about neuroregulation prove correct, additional genetic polymorphisms in detoxification enzymes may lower the threshold for developing chemical intolerances in certain cases. For example, reduced phenolsulphotransferase activity has been demonstrated in some patients with dietary migraine,[52] and low pulmonary sulphite oxidase levels have been reported in asthmatics sensitive to sulphite preservatives.[53] However, this is unlikely to be the rule. We have studied salicylate pharmacodynamics in 26 patients with aspirin-sensitive urticaria and found them to be no different from normal controls (unpublished observations). The significance of other changes such as altered intestinal permeability remain to be determined.[54]

CONCLUSIONS

Is it ''psychosomatic''?

This is a question which frequently arises in relation to all of the conditions discussed above, and which therefore deserves careful consideration. Clinical experience in patients with food intolerance reveals a complex relationship with psychological stress. On the one hand, certain individuals find that acutely stressful situations can aggravate or precipitate symptoms, and during periods of chronic stress the threshold for food reactions may be lowered. This phenomenon is most likely to occur in patients presenting with constitutional symptoms, less so in those with uncomplicated headaches or irritable bowel syndrome, and is rare in those with isolated urticaria. Conversely, patients can experience neuropsychiatric symptoms in response to food chemicals, and in these circumstances they often perceive a given situation as more stressful than it would otherwise have been. Thus, in the sense that psychological and physical symptoms can interact, we could consider the disorders involved as being "psychosomatic", at least in some individuals.

However, it is worth dwelling for a moment on the meaning of this term. In a thoughtful review, Lipowski[55] has drawn a semantic and philosophical distinction between what he regards as the now obsolete idea of psychogenesis, and the more holistic view of biopsychosocial relationships in health and disease. He criticizes application of the term *psychosomatic disorder* to "...any somatic disease or dysfunction in which psychologic factors are postulated to play a necessary or sufficient causal role", suggesting that this has given rise to pointless and misleading polemics. He regards the term as being "...incompatible with the doctrine of multicausality which constitutes a core assumption in the field of psychosomatic medicine" and advocates that it be discarded.

Although this view is reasonably widely accepted nowadays, it remains problematic. Leaving aside the trivial truism that "biopsychosocial" relationships exist in all disease, the doctrine of multicausality does not distinguish between primary causation (sine

qua non) and other factors, and it introduces the likelihood that non-causal associations will be mistakenly accorded aetiological status.[56] Witness the confusion surrounding the role of personality factors in pathogenesis of irritable bowel syndrome,[20] where it is now clear that psychosocial variables correlate with health care seeking behaviour rather than with the disease itself.[57] Moreover, multicausality still retains the dualist notion of psychogenesis in that states of mind, even though they may not be considered necessary or sufficient, are nonetheless imagined to contribute in some more-or-less direct way to the development of physical disease. Though popular, this notion must be regarded as speculative, at best.[58,59]

In individual cases, the idea of multicausality encourages practitioners to extract post hoc clinical evidence to support the belief that "stress" is an aetiological factor. Consequently, if a patient admits to neuropsychiatric symptoms and a perception of stress, it becomes an easy matter to confuse correlation with causation,[56,57] or to diagnose primary psychiatric disease where none exists.[60,61] On the other hand, if a patient denies any significant emotional symptoms, this in itself may be taken as evidence of deep-seated psychopathology. Finally, obscuring the fact that the evidence cannot always be made to fit the theory, vague diagnostic labels such as "masked depression" are applied.

What should the "diagnosis" be?

Diagnostic labeling can serve many useful purposes for both patients and doctors, including socio-cultural, conceptual, prognostic and therapeutic ones. However, it can also serve as a cloak for ignorance, prejudice or misguided belief.[62] Nowhere, perhaps, is this more evident than in patients with chronic fatigue and food intolerance, where the diagnostic label used generally reflects the biases of the observer rather than any real understanding of the underlying pathophysiology (Table 7).[63-75]

Kendell[76] argues that "chronic fatigue syndrome" is often a misdiagnosis in patients who, in reality, have an unrecognized depressive illness which would benefit from appropriate treatment. Our clinical experience does not bear this out, being more in line with the view that when depression is evident it is usually secondary.[77] Many of our patients have, in fact, had a trial of antidepressant therapy at some stage, either before or after referral for dietary investigation, but a favourable response is very much the exception rather than the rule. Indeed, as with most drugs acting on the CNS, such patients often experience exaggerated side-effects and may be forced to abandon treatment as a result. Whilst we share Kendell's general view that there is probably no fundamental distinction between depressive illness and other kinds of "organic" illness,[76] forcing patients with vaguely similar neuropsychiatric symptoms, but no primary mood change, into the same diagnostic category seems more hindrance than help, both from a conceptual and a practical point of view.

Table 7

Practitioner	Diagnosis
Microbiologist	Post-viral fatigue syndrome Chronic EBV infection
Immunologist	Immune dysfunction syndrome
Rheumatologist	Fibromyalgia syndrome
Internist	Chronic hyperventilation
General Practitioner	Bored housewife syndrome Yuppie Flu
Psychiatrist	Somatization disorder Depression
Neurologist	Myalgic encephalomyelitis Hysteria
Allergist	Food allergy / intolerance
Clinical ecologist	20th century syndrome
Orthomolecular	Hypoglycaemia Vitamin deficiency
Naturopath	Candida hypersensitivity

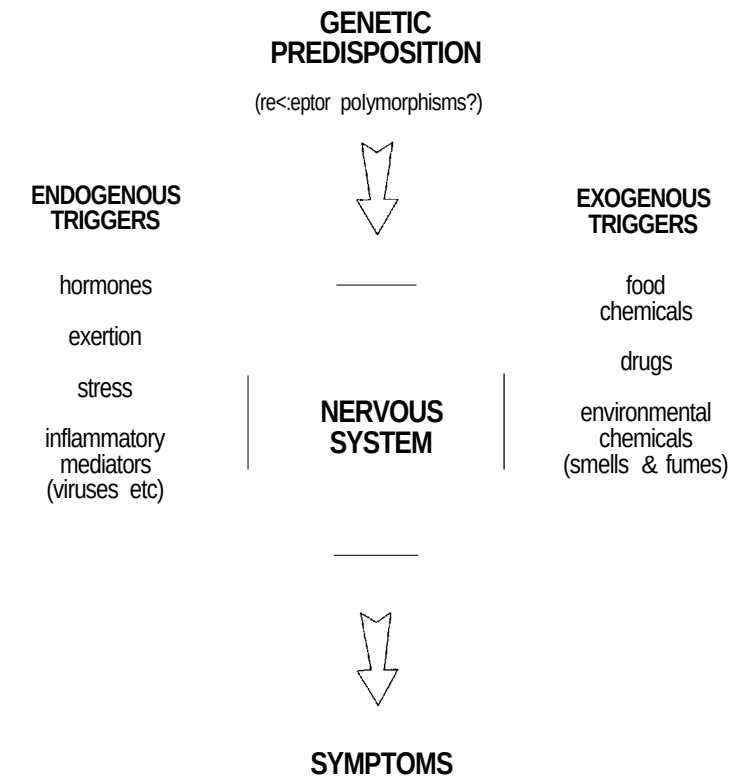
Another psychiatric designation sometimes applied to patients with chronic fatigue syndrome[78] is "somatoform disorder", one of the subtypes of what used to be called hysteria. Here there exist even greater conceptual problems. Lipowski[79] defines so-

matization as "...a tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them. It is usually assumed that this tendency becomes manifest in response to psychosocial stress brought about by life events and situations." Central to the definition is the patient's persistent search for a medical diagnosis and treatment"...despite doctors' reassurances that physical illness cannot account for their symptoms."79

> Thus, the entire concept of somatization is based on the false premise that biomedical science has now reached the point where all physical causes of illness are known, and can be excluded with certainty by a competent physician.[80]

Failure to appreciate the extent of our collective limitations in this regard can lead to false value judgements about illness behaviorsl and about the legitimacy (or otherwise) of the sick role. To quote Lipowski again: "Somatization ... involves both mind and body, and, as a mimicry of 'real' diseases, is a state of being that is neither wellness nor 'legitimate' sickness.'"79 From our own perspective, a hint of the underlying fallacy can be discerned in the findings of one series where nearly 50% of patients judged to have a chronic somatoform disorder reported "food intolerances" amongst their symptoms.[63]

We are often asked by our own patients with chronic fatigue, in whom food intolerance is found to be a significant factor, "What do I really have, doctor, 'food intolerance' or 'chronic fatigue syndrome'?" Whilst recognizing the importance of supplying patients with a 'diagnosis' for ease of communication with doctors, employers, family and friends, we nevertheless prefer to offer an operational description where possible. In doing so, we try to convey the idea that neither food intolerance nor chronic fatigue syndrome should be considered disease entities.[82] Rather, we regard food chemicals (like drugs, hormones, viruses, stress) as one of many possible exogenous or endogenous triggers capable of provoking symptoms; and we regard chronic fatigue syndrome as a cluster of neurological symptoms which can arise in response to one or more such stimuli in predisposed people, as illustrated below. Delineation of more meaningful diagnostic terminology must await a deeper understanding of the underlying molecular pathology.



References

1. LessofMH. 'Clinical reactions to food'. John Wiley & Sons, Chichester, 1983.

2. LessofMH, Gray JR, Hoffenberg R, et al. Food intolerance and food aversion. J Roy Coll Physicians Lond 1984;18:83-123.

3. Sampson HA. IgE-mediated food intolerance. J Allergy Clin Immunol 1988;81:495-504.

4. Loblay RH, Swain AR. Food intolerance. In: 'Recent Advances in Clinical Nutrition'. Eds. Wahlqvist ML and Truswell AS, John Libbey, London, Vo!. 2, 1986. pp 169-177.

5. Johns T. 'With bitter herbs they shall eat it: Chemical ecology and the origins of human diet and medicine'. University of Arizona Press, Tucson, 1990.

6. Swain AR, Dutton S, Truswell AS. Salicylates in food. JAm Diet Ass 1985;85:950-60.

7. Maga JA. Amines in foods. CRC Crit Rev Food Sci Nutr 1978;10:373-403.

8. Filer LJ, Garattini S, Kane MR, Reynolds WA, Wurtman RJ. Glutamic acid: Advances in biochemistry and physiology. Raven Press, New York, 1979.

9. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. Ann IntMed 1988;108:387-9.

10. Behan PO, Behan WMH, Bell EJ. The postviral fatigue syndrome - an analysis of the findings in 50 cases. J infection 1985;10:211-22.

11. Lloyd A, Wakefield D, Boughton C, Dwyer J. Immunological abnormalities in the chronic fatigue syndrome. Med J Aust 1989;151:122-4.

12. Lance JW, Lambert GA, Goadsby PJ, Zagami AS. 5-Hydroxytryptamine and its putative aetiological involvement in migraine. Cephalalgia 1989;9(suppl 9):7-13.

13. Ribiero CAF, Cotrim MD, Morgadinho MT, Ramos MI, Santos ES, de Macedo TdRA. Migraine, serum serotonin and platelet 5-HT2 receptors. Cephalalgia 1990;10:213-9.

14. Moskowitz MA. Basic mechanisms in vascular headache. Neurology Clinics of North America 1990;4:801-15.

15. Edvinsson L, Goadsby PG, J ansen I, U dman R. Perivascular peptide transmitters: Innervation and release in migraine. Cephalalgia 1989;9(suppl10):15-6.

16. Nicolodi M, Bianco ED. Sensory neuropeptides (substance P, calcitonin gene-related peptide) and vasoactive intestinal polypeptide in human saliva: their pattern in migraine and cluster headache. Cephalalgia 1990;10:39-50.

17. Leao AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944;7:379-90.

18. Welch KMA, D'Andrea G, Tepley N, Barkley G, RamadanNM. The concept of migraine as a state of central neuronal hyperexcitability. Neurology Clinics of North America 1990;8:817-28.

19. Malmgren R. The central serotoninergic system. Cephalalgia 1990;10:199-204.

20. Kellow JE, Langeluddecke PM. Advances in the understanding and management of the irritable bowel syndrome. Med J Aust 1989;151:92-9.

21. Fox JET. Control of gastrointestinal motility be peptides: Old peptides, new tricks - new peptides, old tricks. Gastroenterology Clinics of North America 1989;18:163-77.

22. Sternini C. Structural and chemical organization of the myenteric plexus. Ann Rev Physiol 1988;50:81-93.

23. Tache Y, Garrick T, Raybould H. Central nervous system action of peptides to influence gastrointestinal motor function. Gastroenterology 1990;98:517-28.

24. Whorwell PJ, Lupton EW, Erduran D, et al. Bladder smooth muscle dysfunction in patients with irritable bowel syndrome. Gut 1986;27:1014-47.

25. White A, UptonA, Collins SM. Is irritable bowel syndrome the asthma of the gut? Gastroenterology 1988;94:A494.

26. Kellow JE, Miller LJ, Phillips SF et al. Altered sensitivity of the gall bladder to cholecystokinin octapeptide in irritable bowel syndrome. Gut 1988;29:1236-43.

27. Lemanske RF, Sampson HA. Adverse reactions to foods and their relationship to skin diseases in children. Adv Pediatr 1988;35:189-218.

28. Wasserman SI. Chronic urticaria - a frustrating but increasingly understandable disorder. West J Med 1990;152:292-3.

29. Church MK, Lowman MA, Rees PM et al. Mast cells, neuropeptides and inflammation. Agents Actions 1989;27:8-16.

30. Lembeck F, Holzer P. Substance P as neurogenic mediator of antidromic vasodilatation and neurogenic plasma extravasation. Arch PharmacoI1979;31O:175-83.

31. Foreman JC. Substance P and calcitonin gene-related peptide: effects on mast cells and in human skin. Int Archs Allergy Appl ImmunoI1987;82:366-71.

32. Pearce FL, Kassessinoff TA, Liu WL. Characteristics of histamine secretion induced by neuropeptides: implications for the relevance of peptide-mast cell interactions in allergy and inflammation. IntArch Allergy Appl ImmunoI1989;88:129-31.

33. Arzubiaga C, Morrow J, Roberts J, Biaggioni I. Neuropeptide Y, a putative cotransmitter in noradrenergic neurons, induces mast cell degranulation but not prostaglandin D2 release. J Allergy Clin ImmunoI1991;87:88-93.

34. Newson B, Dahlstrom A, Enerback L, Ahlman H. Suggestive evidence for a direct innervation of mucosal mast cells. An electron microscopic study. Neuroscience 1983;10:565-70.

35. Skofitsch G, Savitt JM, Jacobovitz DM. Suggestive evidence for a functional unit between mast cells and substance P fibers in the rat diaphragm and mesentery. Histochemistry 1985;82:5-8.

36. Bienenstock J, Tomioka M, Matsuda H, Stead RH, Quinonez G, Simon GT, Coughlin MD, Denburg JA. The role of mast cells in inflammatory processes: Evidence for nerve/mast cell interactions. Int Archs Allergy Appl Immun 1987;82:238-43.

37. Foreman JC. Neuropeptides and the pathogenesis of allergy. Allergy 1987;42:1-11.

38. Church MK, Lowman MA, Robinson C, Holgate ST, Benyon C. Interaction of neuropeptides with human mast cells. Int Arch Allergy Appl Immunol 1989;88:70-8.

39. Smedley H, Katrak M, Sikora K, Wheeler T. Neurological side effects of recombinant human interferon. Br Med J 1983;286:262-4.

40. McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. An investigation in a trial of recombinant alpha interferon in hepatitis B carriers. Lancet 1987;ii:1175-9.

41. Snyder SH. Receptors, neurotransmitters and drug responses. N Engl J Med 1979;300:465-72.

42. Furness JB, Morris JL, Gibbins IL, Costa M. Chemical coding of neurons and plurichemical transmission. Ann Rev Pharmacol Toxicol 1989;29:289-306.

43. Kow L-M, Pfaff DW. Neuromodulatory actions of peptides. Ann Rev Pharmacol Toxicol 1988;28:163-88.

44. Hill SJ, Kendall DA. Cross-talk between different receptor-effector systems in the mammalian CNS. Cellular Signalling 1989;1:135-41.

45. Olney JW. Excitotoxic food additives - relevance of animal studies to human safety. Neurobehav Toxicol Teratol 1984;6:455-62.

46. Olney JW. Excitotoxic amino acids and neuropsychiatric disorders. Ann Rev Pharmacol Toxicol 1990;30:47-71.

47. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and non-steroidal anti-inflammatory drugs. J Allergy Clin Immunol 1984;74:617-22.

48. Stevenson DD, Lewis RA. Proposed mechanisms of aspirin sensitivity reactions. J Allergy Clin Immun 1987;80:788-90.

49. Slepian IK, Mathews KP, McLean JA. Aspirin-sensitive asthma. Chest 1985;87:386-91.

50. Rainsford KD. 'Aspirin and the salicylates'. Butterworths, London, 1984.

51. Birnmaumer L. G proteins in signal transduction. Annu Rev Pharmacol Toxicol 1990;30:675-705.

52. Glover V, Littlewood J, Sandler M, Peatfield R, Petty R, Rose FC. Biochemical predisposition to dietary migraine: the role of phenolsulphotransferase. Headache 1983;23:53-8.

53. Jacobsen DW, Simon RA, Singh M. Sulfite-oxidase deficiency and cobalamin protection in sulfite-sensitive asthmatics. J Allergy Clin Immunol 1984;73:135.

54. Paganelli R, Fagiolo D, Cancian M, Sturniolo GC, Scala E, D'Offizi GP. Intestinal permeability in irritable bowel syndrome. Effect of diet and sodium cromoglycate administration. Ann Allergy 1990;64:377-80.

55. Lipowski ZJ. What does the word "psychosomatic" really mean? A historical and semantic inquiry. Psychosomatic Med 1984;46:153-71.

56. Stehbens WE. The concept of cause in disease. J Chron Dis 1985;38:947-50.

57. Smith RC, Greenbaum DS, Vancouver JB, Henry RC, Reinhart MA, Greenbaum RB, Dean HA, Mayle JE. Psychosocial factors are associated with health care seeking rather than diagnosis in irritable bowel syndrome. Gastroenterology 1990;88:293-301.

58. Angell M. Disease as a reflection of the psyche. N Engl J Med 1985;312:1570-2.

59. Hall JG. Emotion and immunity. Lancet 1985;ii:326-7.

60. Nicholson GA, Wilby J, Tennant C. Myasthenia gravis: the problem of a "psychiatric" misdiagnosis. Med J Aust 1986;144:632-8.

61. Rosenhan DL. On being sane in insane places. Science 1973;179:250-8.

62. Skrabanek P, McCormick J. 'Follies and fallacies in medicine'. Prometheus Books, Buffalo, NY, 1990.

63. Woodruff RA, Goodwin DW, Guze SB. Hysteria (Briquet's syndrome). In "Hysteria", ed A Roy, John Wiley, New York, 1982; pp 117-29.

64. Jones JE, Ray CG, Minnich LL, et al. Evidence for active Epstein-Barr virus infection in patients with persistent unexplained illnesses: Elevated anti-early antigen antibodies. Ann Intern Med 1985;102:1-7.

65. Tobi M, Straus SE. Chronic Epstein-Barr virus disease. Ann Intern Med 1985;103:951-3.

66. Buchwald D, Goldenberg DL, Sullivan JL, Komaroff AL. The "chronic active Epstein-Barr virus infection" syndrome and primary fibromyalgia. Arthritis Rheum 1987;30:1132-6.

67. Goldenberg DL, Simms RW, Geiger A, Komaroff AL. High frequency of fibromyalgia in patients with chronic fatigue syndrome seen in primary care practice. Arthritis Rheum. 1990;33:381-7.

68. Wessely S. Old wine in new bottles: neurasthenia and ME. Psychol Med 1990;20:35-53.

69. Pearson DJ, Rix KJB, Bentley SJ. Food allergy: How much in the mind? A clinical and psychiatric study of suspected food hypersensitivity. Lancet 1983;i:1259-61.

70. Stewart DE, Raskin J. Psychiatric assessment of patients with "20th century disease" ("total allergy syndrome"). Can Med Assoc J 1985;133:1001-6.

71. Terr AI. Clinical ecology. J Allergy Clin Immunol 1987;79:423-6.

72. Ferguson A. Food sensitivity or self-deception? N Engl J Med 1990;323:476-8.

73. Hofeldt FD, Adler RA, Herman RH. Postprandial hypoglycemia. Fact or fiction? J Am Med Ass 1975;233:1309.

74. Best JD. Reactive hypoglycemia in perspective. Patient Management 1984;8:113-21.

75. Crook WG. 'The yeast connection'. Professional Books, Jackson, Tennessee. 2nd ed, 1984.

76. Kendell RE. Chronic fatigue, viruses and depression. Lancet 1991;337:160-3.

77. Hickie I, Lloyd A, Wakefield D, Parker G. The psychiatric status of patients with chronic fatigue syndrome. Br J Psychiatry 1990;156:534-40.

78. Kruesi MJP, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue syndrome. J Clin Psychiatry 1989;50:53-6.

79. Lipowski ZJ. Somatization: the concept and its application. Am J Psychiatry 1988;145:1358-68.

80. MeIntyre N, Popper K. The critical attitude in medicine: the need for a new ethics. Br Med J 1983;287:1919-23.

81. Pilowski I. Abnormal illness behaviours and their treatments. Med J Aust 1990;153:346-8.

82. Jennings D. The confusion between disease and illness in clinical medicine. Can Med Assoc J 1986;135:865-70.