

**Chapter 8**

**Patient-centered Care: Antecedents, Triggers, and Mediators**

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*It is more important to know what person has the disease than which disease the person has.*
—William Osler

The purpose of this chapter is to present an *organizational structure* for assessment of patients as unique individuals, an approach I have called person-centered diagnosis. The goal of person-centered diagnosis is to enable healers to develop individualized treatment plans that are based upon an understanding of the physiological, environmental, and psychosocial contexts within which each person’s illnesses or dysfunctions occur. The information you need to effectively apply this organizational structure fills the remainder of this textbook. My goal here is to describe and illustrate the structure. To create it, you must start by eliciting all of the patient’s concerns. In actively listening to the patient’s story, you attempt to discover the antecedents, triggers and mediators that underlie symptoms, signs, illness behaviors, and demonstrable pathology. Functional medicine is based upon treatment that is collaborative, flexible, and focused on the control or reversal of each person’s individual antecedents, triggers and mediators, rather than the treatment of disease entities.

**Eliciting the Patient’s Story**

The first step in patient-centered care is eliciting the patient’s story in a comprehensive manner. It is the functional medicine practitioner’s job to know not just the ailments or their diagnoses, but the physical and social environment in which sickness occurs, the dietary habits of the person who is sick (present diet and pre-illness diet), his beliefs about the illness, the impact of illness on social and psychological function, factors that aggravate or ameliorate symptoms, and factors that predispose to illness or facilitate recovery. This information is necessary for establishing a functional treatment plan.

The importance of understanding the patient’s experience of his/her illness cannot be overemphasized. Extensive research on doctor-patient interactions indicates that doctors who fail to pay attention to the patient’s concerns miss important clinical information. The conventional diagnostic paradigm, differential diagnosis, leads doctors to ignore or denigrate information that patients consider important, or that influences individual prognosis. Not only does this ignorance impair the effectiveness of treatment, it generates considerable dissatisfaction among patients. Extensive research done within the context of conventional medical care reveals what most patients know: doctors do not pay enough attention to what their patients have to say. A study done at the University of Rochester found that most patients have three reasons for visiting a physician, are interrupted within 18 seconds of starting to tell their stories, and never get the chance to finish. Although doctors excuse this behavior by citing lack of time, it would have taken an average of one minute and rarely more than three minutes for a complete list of problems to be elicited.

Even when doctors know what their patients’ concerns are, they typically ignore them. Most patients have different ideas about their illnesses than their doctors and some form of clarification or negotiation is needed for an effective therapeutic alliance to be established. A study that carefully analyzed taped transcripts of visits to a medical clinic found that patients attempted
to clarify or challenge what their doctor had said in 85% of the visits. Their requests were usually ignored or interrupted. Understanding the patient’s perspective allows the doctor to work in a collaborative way with patients, giving information that helps the patient make healthful choices. The more information the patient receives from the doctor and the more actively the patient is involved in making decisions about treatment, the higher the level of mutual satisfaction, and the better the clinical outcome. A systematic review of randomized clinical trials and analytic studies of physician-patient communication confirmed a positive influence of quality communication on health outcomes. Such a collaborative relationship depends upon the practitioner recognizing and acknowledging the patient’s experience of the illness. Useful questions to ask include:

- How are you hoping that I can help you today?
- What do you believe is the source of your problems?
- What kind of treatment are you looking for?
- What do you most fear about your illness?
- What impact have your symptoms had on your life?

Organizing and Analyzing the Patient’s Story

What modern science has taught us about the genesis of disease can be represented by three words: triggers, mediators, and antecedents. Triggers are discrete entities or events that provoke disease or its symptoms. microbes are an example. The greatest scientific discovery of the 19th century was the microbial etiology of the major epidemic diseases. Triggers are usually insufficient in and of themselves for disease formation, however. Host response is an essential component. Identifying the biochemical mediators that underlie host responses was the most productive field of biomedical research during the second half of the 20th century. Mediators, as the word implies, do not “cause” disease. They are intermediaries that contribute to the manifestations of disease. Antecedents are factors that predispose to acute or chronic illness. For a person who is ill, they form the illness diathesis. From the perspective of prevention, they are risk factors. Knowledge of antecedents has provided a rational structure for the organization of preventive medicine and public health. Medical genomics seeks to better understand disease by identifying the phenotypic expression of disease-related genes and their products. The application of genomic science to clinical medicine requires the integration of antecedents (genes and the factors controlling their expression) with mediators (the downstream products of gene activation). Mediators, triggers, and antecedents are not only key biomedical concepts, they are also important psychosocial concepts. In person-centered diagnosis, the mediators, triggers, and antecedents for each person’s illness form the focus of clinical investigation.

Antecedents and the Origins of Illness

Understanding the antecedents of illness helps the physician understand the unique characteristics of each patient as they relate to his or her current health status. Antecedents may be thought of as congenital or developmental. The most important congenital factor is gender: women and men differ markedly in susceptibility to many disorders. The most important developmental factor is age; what ails children is rarely the same as what ails the elderly. Beyond these obvious factors lies a diversity as complex as the genetic differences and separate life experiences that distinguish one person from another.

Congenital factors may be inherited or acquired in utero. They can most readily be evaluated from a comprehensive family history, including mother’s health before and during pregnancy. Genomic analysis, which is now commercially available, can supplement the family health history as a tool for investigating unique nutritional needs or individual variability in sensitivity to environmental toxins. The commonest single gene disorders in North America, celiac disease and hemochromatosis, may be confirmed by the presence of genetic markers, but should first be suspected from abnormalities in routine lab tests. Elevated serum ferritin concentration or transferrin saturation should prompt genetic testing for the alleles associated with hereditary hemochromatosis. Increased small intestinal permeability, as measured by the inexpensive, non-invasive and under-utilized lactulose/mannitol challenge test, has a sensitivity approaching 100% for untreated celiac disease. Abnormal intestinal permeability should prompt the measurement of celiac-specific immune markers in patients with chronic fatigue, autoimmune disorders, or chronic gastrointestinal complaints of any type.

Normal intestinal permeability in patients consuming gluten almost always excludes celiac disease as a consideration; however, this may not necessarily be the
case for other gluten-sensitive disorders. Because celiac disease and gluten-sensitive disorders are common, have protean manifestations, and can be well controlled by nutritional interventions, intestinal permeability should be a routine component of the laboratory testing for antecedents of illness. The treatment of choice for frank hemochromatosis is phlebotomy, but mild iron overload without frank hemochromatosis is more common than the full-blown disease. These patients generally have only one of the alleles associated with the disease, but have elevated transferrin saturation and/or ferritin. They are not treated with phlebotomy, and should be treated with dietary interventions. They should not take iron or vitamin C supplements, because vitamin C reduces iron to its more toxic form.

Some familial disorders may reflect intra-uterine rather than genetic influences. Twin studies of hypertension, for example, indicate a higher concordance for blood pressure between identical twins with a common placenta than identical twins with separate placentas. Presumably, the shared placenta mediates subtle nutritional influences that affect a tendency toward chronic illness in adulthood.

Post-natal developmental factors that govern the predisposition to illness include nutrition, exposure to toxins, trauma, learned patterns of behavior, and the microbial ecology of the body. Sexual abuse in childhood, for example, is associated with an increased risk of abdominal and pelvic pain syndromes among women. Recurrent otitis media increases the risk of a child developing attention deficit disorder, an effect that is not associated with hearing loss but may result from the effects of antibiotics on the microbial ecology of the gut.

Precipitating events are critical antecedents that closely precede the development of chronic illness. They represent a boundary in time: before this event, the person was considered healthy; since the event, the person has become a patient. Understanding the nature of the precipitating event may aid in unraveling the triggers and mediators that maintain the state of illness. The commonest precipitating events among my patients are a period of severe psychosocial distress, an acute infection (sometimes treated with antibiotics), exposure to environmental toxins at work or home, or severe nutrient depletion related to illness or crash dieting. Useful questions for uncovering precipitating events include:

- When is the last time you felt really well for more than a few days at a time?
- During the six months preceding that date, did you experience any illness or major stress, change your use of medication or dietary supplements, or make any significant life changes?

Other publications of this author present cases in which cryptogenic illness was found to be precipitated by foreign travel, antibiotic use, dietary changes, smoldering infection, or the illness of a spouse.

**Triggers and the Provocation of Illness**

A trigger is anything that initiates an acute illness or the emergence of symptoms. The distinction between a trigger and a precipitating event is relative, not absolute; the distinction helps organize the patient’s story. As a general rule, triggers only provoke illness as long as the person is exposed to them (or for a short while afterward), whereas a precipitating event initiates a change in health status that persists long after the exposure ends. Common triggers include physical or psychic trauma, microbes, drugs, allergens, foods (or even the act of eating or drinking), environmental toxins, temperature change, stressful life events, adverse social interactions, and powerful memories. For some conditions, the trigger is such an essential part of our concept of the disease that the two cannot be separated; the disease is either named after the trigger (e.g., “Strep throat”) or the absence of the trigger negates the diagnosis (e.g., concussion cannot occur without head trauma). For chronic ailments like asthma, arthritis, or migraine headaches, multiple interacting triggers may be present. All triggers, however, exert their effects through the activation of host-derived mediators. In closed-head trauma, for example, activation of NMDA receptors, induction of nitric oxide synthase (iNOS), and liberation of free intra-neuronal calcium determine the late effects. Intravenous magnesium at the time of trauma attenuates severity by altering the mediator response. Sensitivity to different triggers often varies among persons with similar ailments. A prime task of the functional practitioner is to help patients identify important triggers for their ailments and develop strategies for eliminating them or diminishing their virulence.

Although the identification and elimination of triggers is not a foreign concept in conventional medicine, many physicians neglect the search. A study was
conducted by telephone in which practicing physicians were asked how they would treat a new patient with abdominal pain, who had a recent diagnosis of gastritis made by a specialist in another town. Almost half were ready to put the patient on acid-lowering therapy without asking about the patient’s use of aspirin, alcohol or tobacco, all of which are potential triggers for gastritis. The authors of the study concluded, “In actual practice, ignoring these aspects of the patient may well have reduced or even negated the efficacy of other therapeutic plans implemented.”

Mediators and the Formation of Illness

A mediator is anything that produces symptoms, damage to tissues of the body, or the types of behaviors associated with being sick. Mediators vary in form and substance. They may be biochemical (like prostanoids and cytokines), ionic (like hydrogen ions), social (like reinforcement for staying ill), psychological (like fear), or cultural (like beliefs about the nature of illness). A list of common mediators is presented in Table 8.1. Illness in any single person usually involves multiple interacting mediators. Biochemical, psychosocial, and cultural mediators interact continuously in the formation of illness.

Cognitive/emotional mediators determine how patients appraise symptoms and what actions they take in response to that appraisal. They may even modulate the symptoms themselves. People in, for example, experience more pain when they fear that pain control will be inadequate than when they believe that ample pain management is available.

Perceived self-efficacy (the belief in one’s ability to cope successfully with specific problems) is a cognitive mediator that determines coping with illness. People with a high degree of health self-efficacy usually adapt better to chronic disease, maintaining higher levels of activity, requiring lower doses of pain medication, adopting healthier lifestyles, and cooperating with prescribed therapies, compared to people with low self-efficacy. Self-management education is designed to enhance self-efficacy, and has been shown to improve the clinical outcome for patients with several types of chronic disease, including asthma, arthritis, and diabetes.

The biochemical mediators of disease listed in Table 8.1 are best known for their ability to promote cellular damage. Most are organized into circuits and cascades that sub-serve homeostasis and allostasis. In these networks, each mediator is multi-functional and most functions involve multiple mediators, so that redundancy is the rule, not the exception. The most striking characteristic of biochemical mediators is their lack of disease specificity. Each mediator can be implicated in many different, apparently unrelated diseases, and every disease involves multiple chemical mediators in its formation.

Mediator networks that regulate inflammatory and neuroendocrine stress responses have been the subject of intensive research with important clinical implications. A detailed discussion of these networks is outside the scope of this chapter, but they are addressed in Chapters 19, 23, 27, and 32; see the index for further cross-referencing. Comprehensive reviews have appeared elsewhere. Within the framework of functional medicine, a key feature of biochemical mediators is the natural rhythm of mediator activity, which is strongly influenced by the common components of life: diet, sleep, exercise, hygiene, social interactions, solar and lunar cycles, age, and sex. Aging, illness, and chronic psychological distress upregulate activity of the inflammatory and neuroendocrine-stress response networks. Regular physical activity downregulates both.
Integrating the Patient’s Story

After listening to the concerns that led each patient to seek a consultation in functional medicine, the clinician makes a series of distinctions:

1. For patients whose main concern is optimal health and prevention, ask about present and past health problems and the family health history. If these supply no indication of illness susceptibility, then turn your attention to risk factors for future illness: weight, fitness, type and level of physical activity, dietary pattern, sleep habits, use of alcohol, drugs, tobacco, firearms, environmental exposures at home and work, travel, sources of stress and pleasure, degree of involvement with others, spiritual beliefs and practices, sexual relationships, hopes and fears for the future.

2. For patients with an active health problem, always ask, “What was your health like before this problem began?” An intake questionnaire that asks about previous health problems is also helpful, because it gathers information in a different fashion concerning what the patient was like prior to the present illness. Such a tool is condition-specific, not open-ended. The two approaches complement one another.

   a. Some patients will say that they were really healthy prior to their present illness. In that case, look for a precipitating event. If you or the patient can identify one, then ask about ongoing triggers that bear some relationship to the precipitating event. For example: if the precipitating event was marital or job stress, focus on stress-related psychological triggers. If the precipitating event was an environmental exposure, focus on ongoing exposures to volatile chemicals or mold.

   b. The most challenging patients will usually indicate that their health was poor even before their present illness. In that case, take a detailed, chronological history from birth to the present that includes information about early life experience (including illness, injury and abuse), school and work performance, diet, drug and medication use, leisure activities, travel, family life, sexual experiences, habits, life stressors, and places of residence. Because gathering this data can be very time consuming, a self-administered questionnaire completed by the patient before the interview may help to prompt responses and improve memory of remote events. For many patients with complex, chronic health problems, it may be useful to take a detailed life history before seeking detailed information about present symptoms. Problems that emerge from such a review have to be addressed for a successful outcome of treatment. Dealing with the present concerns by themselves almost never succeeds for patients in this group.

Whatever rapport you establish with patients initially, maintaining the therapeutic relationship usually depends upon significant improvement in symptoms or in a sense of well-being within a few days to a few weeks of the initial evaluation. This is most efficiently achieved by addressing the triggers that provoke symptoms and helping the patient decrease exposure to them. When triggers cannot be identified or avoided, then symptomatic improvement must rest on control of mediator activation. A combination of the two will usually produce the most satisfactory long-term benefits.

Assessment of Triggers

A comprehensive search for triggers requires that you know the following about your patient: each drug—prescription, over-the-counter or recreational—that the patient has used and when; nutritional habits and each dietary supplement used and when; what effects the patient noted from the use of each substance; sources of stress—life events, environmental exposures, thoughts or memories, and social interactions—and when they occurred in relation to symptoms. Elicit the patient’s own ideas about possible triggers by asking, “What do you think causes or aggravates your symptoms?” The patient’s observations may be insightful and accurate in ascribing causality. Of course the patient’s—and the clinician’s—observations can also mislead, or focus on non-essential factors. Teach patients to challenge their own observations by looking for consistency and replicability, wherever possible. Suggest alternative theories for the patient to consider and explain that the search for triggers works best as a collaborative effort between patient and doctor. The patient’s ability to recognize triggers is an important step in self-care.
Food and environment supply important triggers for the practice of functional medicine. Food intolerance is a very common phenomenon, reported by 33% of the population in one large study. Relatively few of these reactions (4–14%) are due to true food allergies. Most food intolerance has no clear immunologic basis. Mechanisms include sensitivity to the pharmacological effect of alkaloids, amines or salicylates in food. Hista-
mine poisoning from scombroid fish and tyramine-induced headache are dramatic examples. Although most food intolerance is short-lived, severe chronic illness can occur, and the food trigger may elude identification unless the physician starts the investigation with a high index of suspicion. Gluten intolerance, with its protean manifestations, is probably the best example. Affecting about 2% of people of European ancestry, gluten intolerance is common and often unrecognized. In addition to being the essential trigger for celiac disease, gluten sensitivity may be manifest in patients with neurological disorders of unknown cause, cerebellar degeneration, dermatitis herpetiformis, failure to thrive, pervasive developmental delay, inflammatory arthritis, psoriasis, Sjögren’s syndrome, and schizophrenia. The different presentations of gluten sensitivity may derive from genetic differences among affected patients.

Published studies on food intolerance and your patients’ symptoms may be found through the National Library of Medicine. If the patient has a disease diagnosis, an internet search may reveal previously observed associations between specific foods and the patient’s condition. Access PubMed over the internet (www.pubmed.gov) and run a search that cross-ref-
ences the name of the patient’s condition with “Hypersensitivity, food” and also with “Food, adverse reactions.” Both of these are Medline Subject Headings (MESH). There is no MESH listing for “Food Allergy” or “Food Intolerance.” Your search will be more efficient if you list the patient’s condition as it appears in MESH. A negative search does not eliminate food intolerance as a trigger for the condition being searched, but the number of positive findings may surprise you. Health effects of ambient air quality are as important as those of foods. Numerous studies conducted in U.S. cities demonstrate a close correlation between fine-

1 Medical cybrarian Valerie Rankow (vgr99@optonline.net) has assisted the author with this search strategy and with numerous other, more complex searches.

particle air pollution and daily mortality rates, even at levels of pollution considered safe by the World Health Organization. In the industrialized world, most people spend most of their time indoors, and indoor air pollution has become a serious cause of morbidity. Studies using experimental chambers have shown that volatile organic compounds (VOCs) released from building materials, furnishings, office machines, and cleaning products can cause irritation of the respiratory system in humans and animals at levels which are one hundred times weaker than permissible exposure levels or the World Health Organization Indoor Air Guidelines.

Controlled experiments with people who describe themselves as sensitive to VOCs confirm that VOC exposure causes headache, fatigue, and difficulty concentrating. People who deny such sensitivity also experience symptoms, but do not experience mental impairment when exposed. Air samples of buildings with and without “sick building” complaints have established an association between VOC exposure and human sickness.

A questionnaire can elicit important information about environmental exposures at home and at work. The open-ended question, “Has your work or home environment been a concern to you?” should be accompanied by a checklist of potential exposures.

Microbial triggers for chronic illness present a particular challenge, as exemplified by the many facets of Helicobacter pylori infection. Originally isolated from the gastric mucosa of patients with gastritis and peptic ulcer disease, H. pylori has been implicated in the pathogene-
sis of NSAID gastropathy, gastric carcinoma, lymphoma, and a variety of extra-digestive disorders, including ischemic heart disease, ischemic cerebrovascular disorders, rosacea, Sjögren’s syndrome, Raynaud’s syndrome, food allergy, vitamin B12 deficiency, and open-angle glaucoma. For elderly patients with open-angle glaucoma and incidental H. pylori infection of the stomach, eradication of H. pylori by antibiotics was associated with improved control of glaucoma parameters at two years. The mechanism by which H. pylori aggravates open-angle glaucoma is unknown, but may result from the ability of H. pylori colonization of the gastric tract to trigger the local and systemic release of platelet-activating factor, inflammatory cytokines, and vasoactive substances.

In the case of untreated H. pylori infection, non-
invasive screening tests, including serum antibodies,
stool antigens, and C-14 breath testing, are available. For other types of infection, inquiring about the previous response of a given symptom or symptom complex to antibiotics may be useful. In 1988, physicians at the University of Minnesota conducted a study in which they administered intravenous cephalosporins to patients with various types of arthritis who also manifested antibodies to *Borrelia burgdorferi*. Most of these patients were not thought to have Lyme disease. Some met diagnostic criteria for rheumatoid arthritis, some for osteoarthritis, and some for spondyloarthropathies. The response to antibiotics was quite variable and ranged from no response to dramatic and sustained improvement. The authors noted that improvement in arthritis following antibiotics was not related to the patient’s clinical diagnosis or the level of anti-*Borrelia* antibody. The best predictor of a positive response to the experimental treatment was a previous history of improvement of arthritis associated with the use of antibiotics.91

The most comprehensive way to ask the antibiotic question is: “During the time you have had symptom X, have you taken antibiotics for any reason? Which antibiotic? Did symptom X change while you were taking the drug?” Among patients with chronic diarrhea of unknown cause, for example, some will report that their gastrointestinal symptoms improved when taking a specific antibiotic; others will report that they worsened. The first case suggests that bacteria or protozoa sensitive to the antibiotic may be causally related to the patient’s gastrointestinal problems. Repeating the antibiotic prescription can establish if this response is replicable. If so, therapy can focus on treating the microbe and understanding why a single course of antibiotics was ineffective. The second case suggests that depletion of bacteria by antibiotics and concomitant increase in antibiotic-resistant organisms, including yeasts, may be contributing to diarrhea, and treatment can focus on restoration of normal intestinal flora.

**Assessment of Psychosocial Mediators**

Useful questions for eliciting a person’s beliefs about his/her illness are:

- What do you think has caused your problem?
- What do you most fear about your problem?
- How much control do you think you have over your symptoms?

Useful questions for eliciting information about the nature and sources of social support include:

- Are there people in whom you can confide?
- How satisfied are you with your marriage/family/social life?
- How much support do you receive in dealing with your health problems?
- How often do you feel loved or cared for?

**Assessment of Biochemical Mediators**

Understanding the biochemical alterations associated with a conventional disease diagnosis can be helpful in understanding the biochemical mediators of each person’s illness. Inflammation is believed to play a critical role not only in response to infection and in the classic inflammatory diseases, but also in the pathogenesis of coronary artery disease, diabetes, cancer, depression, and the negative health effects associated with obesity and with aging.92,93,94,95,96,97,98 The orchestration of mediator signals in the inflammation and neuroendocrine-stress networks, as they interact with one another, is critical for normal physiological functions (e.g., the architecture of sleep, the repair of injury, and the response to infection), and for the dysfunctional physiology central to the pathogenesis of most of the major chronic diseases.99,100,101

Most chronic disease is associated with chronic inflammation, but the patterns of immune response that underlie inflammation are not always the same. Patients with type 1 diabetes mellitus, Crohn’s disease or any other disorder categorized by granuloma formation or excessive cell-mediated immune responses are likely to have an immune response to common triggers in which the Th1 component is upregulated and not subject to the normal downregulation provided by Th2 activity. Their mediator response to inflammatory stimulation produces excessive levels of gamma-interferon (g-IFN) and interleukin-12 (IL-12), key Th1-related cytokines.102 Patients with severe depression often show a loss of negative feedback in the HPA axis. Urinary free cortisol is elevated; the diurnal pattern may be disrupted, with increased PM cortisol secretion and blunting of dexamethasone suppression. This phenomenon appears to be driven at the level of the hypothalamus, not the adrenals, because spinal fluid corticotropin releasing hormone (CRH) is elevated.103 Several groups of researchers in the late 1990s speculated that impaired synaptic function due to a deficit of omega-3 fatty acids

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may contribute to the CNS dysfunction of patients with depressive illness104,105,106,107 (although some large recent studies do not show the same patterns108,109). Omega-3 fatty acid levels tend to be lower in blood samples than in control populations. The key component appears to be eicosapentaenoic acid (EPA).

To utilize the vast database of available information about biochemical disease mediators, integrative clinicians should consider three strategies. First, maintain up-to-date knowledge of disease pathophysiology by reading reviews in mainstream journals on mechanisms of disease or on specific mediators. In reading these, pay special attention to the types of mediators mentioned and their functions within the networks that involve inflammation, oxidative stress, and neuroendocrine balance. Second, attend workshops and courses that emphasize integrative physiology, sponsored by institutions like IFM, the New York Academy of Sciences, the Center for Mind-Body Medicine, and the American College for Advancement in Medicine.110 Third, employ knowledge of the commonest biochemical imbalances in chronically ill North Americans and the influence of diet, nutrition, and dietary supplements on these imbalances.

Treatment Planning

A functional medicine treatment plan should be collaborative and dynamic. Collaborative means that patient and practitioner work together to set goals and priorities. Dynamic means that the treatment plan is adjusted as needed in response to feedback. Your knowledge of the patient's beliefs about his/her illness and perceived self-efficacy are essential for collaborative treatment. An appropriate therapeutic intervention for dysfunctional beliefs is the giving of information. Patients have an intense need for explanations about the causes of their diseases.111 They want to know how they came to be sick, so that they can attach some meaning to the illness,112 what to expect from the illness, and what they can do to relieve symptoms or speed recovery. Information of this type can reduce anxiety (even when the diagnosis itself is frightening), increase feelings of personal control, and improve the ability to cope with pain. People change their behaviors more readily when they receive information about the importance and the nature of the changes they need to make, help with setting goals, and measuring progress.

The kind of information needed is personal, not statistical. It must answer the question, “What can I do?”

The physician can help patients who are suffering from isolation by calling this isolation to the attention of family members or friends, or by attempting to connect the patient with a support group or community agency. Possibly, there is nothing that can be done to relieve the patient's isolation, but the doctor's awareness and acknowledgment of it can be important to the patient and serve to enhance the therapeutic relationship.113

If potential triggers have been identified, an assessment of the patient's ability to control exposure to them is important. For patients who are reluctant to make major dietary or environmental changes, explain that each avoidance is an experiment that the patient can direct with your guidance. If eliminating foods (and reintroducing those foods as a challenge) has no effect on symptoms or measurable physiologic parameters, do not encourage the patient to persist in the avoidance of those foods, whatever the results of in vitro allergy tests may be. The patient will have enough work to do following a healthy diet. Food intolerance is only meaningful if its effects can be demonstrated in real life.

For microbial triggers, the decision to use prescription antimicrobial drugs or natural products with antimicrobial activity may require negotiation. If the situation is not critical, it is usually worthwhile honoring the patient's preferences and intuition.

Understanding the ways in which mediators are modulated by diet enables creative nutritional therapies to be applied. Salicylic acid, the major metabolite of aspirin, suppresses activation of the nuclear transcription factor NF-κB, an anti-inflammatory effect that is independent of cyclooxygenase inhibition114 and may be responsible for some effects of low-dose aspirin therapy.115 Vegetables are rich sources of natural salicylates and vegetarians may have serum concentrations of salicylic acid as high as those of people ingesting 75 mg of aspirin a day.116

Dietary fatty acids may have profound effects on the network of inflammatory mediators, altering prostanoid synthesis, PPAR activity, and the response to cytokines like IL-1.117,118,119 They have subtler effects on the neuroendocrine-stress response network, modulating neuronal responses to serotonergic and adrenergic transmission.120 Therapy with omega-3 fatty acids provides an excellent example of nutritional modulation of disease activity though alteration of biochemical
mediators.\textsuperscript{121} Three principles can guide this type of therapy. The first utilizes knowledge of the pathophysiology of specific inflammatory and CNS disorders. Using this model, omega-3 therapy has been successfully applied to the treatment of patients with rheumatoid arthritis,\textsuperscript{122} inflammatory bowel disease,\textsuperscript{123} coronary artery disease,\textsuperscript{124} peripheral vascular disease,\textsuperscript{125} dysmenorrhea,\textsuperscript{126} cystic fibrosis,\textsuperscript{127} migraine headaches,\textsuperscript{128} schizophrenia,\textsuperscript{129,130} atopic eczema,\textsuperscript{131} and multiple sclerosis.\textsuperscript{122,133} Because the fatty acid composition of the contemporary Western diet differs significantly from Paleolithic and ancestral diets, reflecting a marked decrease in omega-3 consumption relative to total fat, the response of so many unrelated disorders to EFA supplementation may indicate that EFAs are not merely working as nutraceutical agents, but that EFA dietary status is important for disease pathogenesis.

The second method rests upon the clinical evaluation of an individual’s fatty acid status using clinical parameters that are independent of disease activity. Prasad has stated that the best test for nutritional adequacy is a functional test.\textsuperscript{134} Determine a parameter to follow and measure how administration of the nutrient(s) in question affects that parameter. This method can be applied to the use of EFA therapy in clinical practice. Stevens et al., studying boys with ADHD and a randomly selected population of schoolchildren, found a correlation between low concentrations of omega-3 EFAs, learning and behavior problems, and symptoms associated with EFA deficiency (thirst, dry skin, and dry hair).\textsuperscript{135,136} Evaluating the presence of these symptoms in patients and observing how they change with EFA supplementation is a quick guide to EFA status that may be used clinically to evaluate the EFA contribution to mediator imbalance. This author’s method for doing this has been described elsewhere.\textsuperscript{137} Finally, it is possible to measure the levels of fatty acids in plasma and erythrocyte phospholipids, although guidelines for the level of change in fatty acid profiles needed to produce a known clinical effect have only been reported for patients with rheumatoid arthritis, in whom clinical improvement requires that eicosapentaenoic acid (EPA) account for 5% of fatty acids in plasma phospholipids.\textsuperscript{138}

The successful application of nutritional therapies, especially dietary interventions, and other self-care practices, as part of a therapeutic plan is very helpful in enhancing self-efficacy among patients. Enhancement of self-efficacy should always be a cardinal goal of treatment in functional medicine.

**Summary**

Functional medicine is essentially patient centered, rather than disease centered. A structure is presented for unifying a patient-centered approach to diagnosis and treatment with the fruits of modern clinical science (which evolved primarily to serve the prevailing model of disease-centered care). The core scientific concepts of disease pathogenesis are antecedents, triggers, and mediators. Antecedents are factors, genetic or acquired, that predispose to illness; triggers are factors that provoke the symptoms and signs of illness; and mediators are factors, biochemical or psychosocial, that contribute to pathological changes and dysfunctional responses. Understanding the antecedents, triggers, and mediators that underlie illness or dysfunction in each patient permits therapy to be targeted to the needs of the individual. The conventional diagnosis assigned to the patient may be of value in identifying plausible antecedents, triggers or mediators for each patient, but is not adequate by itself for the designing of patient-centered care.

Applying the model of person-centered diagnosis to patients facilitates the recognition of disturbances that are common in people with chronic illness. Diet, nutrition, and exposure to environmental toxins play central roles in functional medicine because they may predispose to illness, provoke symptoms, and modulate the activity of biochemical mediators through a complex and diverse set of mechanisms. Explaining those mechanisms is a key objective of this textbook.

A patient’s beliefs about health and illness are critically important for self-care and may influence both behavioral and physiological responses to illness. Perceived self-efficacy is an important mediator of health and healing. Enhancement of patients’ self-efficacy through information, education, and the development of a collaborative relationship between patient and healer is a cardinal goal in all clinical encounters.

**References**

Section II
Principles of Functional Medicine


Principles of Functional Medicine

Section II


110. www.acam.org; www.functionalmedicine.org


