Visual Contrast Sensitivity as a Diagnostic Tool

In "Possible Estuary-Associated Syndrome: Symptoms, Vision, and Treatment," Shoemaker and Hudnell (*1*) advocated use of the visual contrast sensitivity (VCS) test as a biomarker to diagnose possible estuary-associated syndrome (PEAS) and to assess response to their proposed treatment regimen. However, the use of VCS as a diagnostic test for PEAS (and subsequent treatment of PEAS with cholestyramine) is not supported by a careful examination of the existing evidence. These points should be clarified.

Shoemaker and Hudnell (*1*) made indirect reference to my work (*2*) in citing Hudnell's publication that suggested a statistical association between VCS deficits in estuary watermen and hours spent at fish kills (*3*). In this paper Hudnell et al. (*3*) used our medical data and their vision data, but reached some conclusions that are not wholly supported by the original historical data. For example, Hudnell et al. (*3*) ruled out the possibility that observed VCS deficits could be due to known neurotoxicants such as solvents or metals, on the basis of our occupational and environmental history responses. These responses were qualitative only and were not sufficiently detailed to distinguish between gasoline poured into a fuel tank (reported by most fishermen) and that used as hand-cleaner (reported by some fishermen). The history elicited did not fully document exposure to other specific and potentially neurotoxic substances that might be found in estuaries, such as hydrogen sulfide from decaying organic materials. [These omissions have been addressed in the current cohort studies in North Carolina (*4*).] Hudnell et al.'s alternative hypothesis (*3*), that the VCS deficits may be

> caused by unknown, non-exposure-related factor(s) or by some other, perhaps more continuous exposure factor(s) associated with the estuaries or geographical area (p. 590)

is more tenable, as is his comment that "given the multiple potential explanations and the study limitations, each of these possibilities should be viewed as tentative (p. 590). Hudnell does concede that in this work, "few study participants met the [Centers for Disease Control and Prevention] case definition for PEAS" (*3*; p. 590). Actually, no subjects met the case description for active PEAS; the prevalence of past symptoms consistent with PEAS was equal in the estuary (exposed) and offshore (unexposed) watermen and consisted of one individual in each group. This suggests that neither current active nor past history of PEAS is likely to be the reason for the intergroup differences in VCS in the estuary versus offshore watermen.

In addition, the (P)EAS description is an epidemiologic concept, meant primarily for surveillance and enumeration purposes. Epidemiologists frequently adopt these concepts to identify potential cases for further clinical evaluation. The description does not represent diagnostic criteria, but is an indication for further evaluation. These descriptions are used to "cast a wide net" and do not indicate that disease is present until further testing verifies a diagnosis. VCS is an indicator of a subclinical process and is not a diagnostic test.

In a study in Virginia, Turf et al. (*5*) did not identify any cases of EAS in the first year of their ongoing prospective cohort study. They observed VCS deficits, which correlated with age, exposure time to estuary waters where *Pfiesteria* organisms may be found more than 50% of the time, and smoking. However, these deficits were not correlated with active (P)EAS, "as no cases were identified during the study. No toxic *Pfiesteria* events nor changes in neurocognivive function were observed" (*5*). Data are accumulating that *Pfiesteria* is enzootic in Atlantic coastal waters, even where ichthyotoxic effects have never been observed. The presence of the organism is not equivalent to presence of its secreted biotoxin, which is produced under rare, and currently incompletely defined, environmental conditions (*6*).

Other studies in North Carolina have evaluated telephone hotline callers with self-reports of symptoms and exposures potentially related to PEAS. As a group, the self-identified "cases" had normal VCS and the control subjects (predominantly non-watermen) had VCS abnormalities (*7*). Hudnell (*8*) concluded that VCS data in this case–control series "do not indicate that visual function was affected by exposure to North Carolina estuaries" (p. 16).

Hudnell et al. (*3*) stated that VCS may be a useful indicator for the diagnosis of PEAS, citing the work of Shoemaker and Hudnell (*1*) as evidence, while Shoemaker and Hudnell (*1*) cited Hudnell et al. (*3*) to support the use of VCS as a diagnostic test, setting up a circular pattern of reasoning. VCS has never been validated as having any correlation to the neuropsychologic (NP) deficits seen in Maryland (*9,10*). The Maryland cases represent the only documented, fully evaluated cluster of environmental PEAS cases to date. Shoemaker and Hudnell (*1*) did not obtain NP testing on their subjects, although this represents the current "gold standard" for verifying PEAS; thus, this is a major shortcoming in their work. [One subject described by Shoemaker and Hudnell (*1*) had been part of the Maryland cohort and was fully evaluated in that context (*9*). That his NP scores were normal on 3-month follow-up by the Maryland research team is not unique or attributable to a specific treatment regimen. Most affected persons in Maryland improved over 3–6 months without any treatment (*11*)]. Symptoms such as confusion and memory problems are seen in a wide variety of clinical situations, ranging from neurotoxin exposure to sick building syndrome to emotional distress. Such symptoms indicate the need for further evaluation and full characterization before the initiation of treatment. VCS is a nonspecific test for neurologic function, which happens to be sensitive to some neurotoxin exposures, such as polychlorinated biphenyls and styrene. It is also affected by common conditions such as alcohol and medication use, learning disabilities, Parkinsonism, Alzheimer's dementia, vitamin deficiencies, and multiple sclerosis (*7*).

An advertisement for Shoemaker's latest book, *Desperation Medicine* (*12*), in the *Carnrick* (Pharmaceuticals) *Quarterly* newspaper (*13*) describes

> how a family practice doctor discovered the neurotoxin basis of chronic Lyme disease, sick building syndrome, *Pfiesteria*, ciguatera and other chronic illnesses (p. 20),

and that

> … a physiologic test of contrast sensitivity pinpoints the true neurotoxic cause of symptoms which are often incorrectly passed off as depression, fibromyalgia, stress and IBS [irritable bowel syndrome] (p. 20).

A successful treatment regimen is promised to readers (*13*). Shoemaker also advocates the use of VCS to screen all patients "who want [the] Lymerix" vaccination for Lyme disease at his chronic fatigue center (*14*); he has written that "many asymptomatic patients with a history of Lyme … have the VCS deficit" (*14*). On his Web site, "Visual Contrast Sensitivity Test Center" (*15*), Shoemaker stated that

> Neurotoxin forming algae are being identified nearly monthly. If you do not have the VCS deficit, response to binding therapy is less [than] 66%. If you have the VCS deficit, response to therapy is over 90%.

He also stated that "unexplainable recurring joint pains of hands, wrists and/or feet" is another symptom of neurotoxin poisoning. Also on this Web site (*15*), Shoemaker discussed the use of the VCS exam to diagnose

pfiesteria, ciguatera, cylindrospermosis (blue green algae in central Florida), sick building syndrome, Lyme disease, and soon chronic fatigue syndrome and chronic soft tissue pathways when our clinical data reach statistical certainty.

He stated that papers on ciguatera, sick building syndrome, and Lyme disease were being prepared, but we have not found these reports in a publications database to date.

On the basis of this evidence, it can only be concluded that *a*) VCS abnormalities are so widespread and nonspecific as to have limited usefulness as a biomarker for any particular condition (especially in the absence of industrial hygiene or environmental documentation regarding the source of exposure); and *b*) there is no evidence that VCS deficits have been observed in persons with current active PEAS verified by accepted, objective NP tests. Of note, passive surveillance efforts to detect PEAS have not recorded any verified cases (*16*) through 2000. Health-care providers have been asked to report suspected PEAS cases to their county health departments in Delaware, Florida, Maryland, North Carolina, South Carolina, and Virginia. The health departments can facilitate the full evaluation of these cases, including NP testing through state health agencies. We hope that the readers of *EHP* will recognize the anecdotal and unsubstantiated nature of the reports in the paper by Shoemaker and Hudnell (*1*), as well as the tremendous amount of medical research yet to be done before either VCS as a biomarker or cholestyramine as a treatment can be appropriately advocated.

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Visual Contrast Sensitivity: Response

We are pleased to respond to the letter from Swinker and Burke regarding our paper "Possible Estuary-Associated Syndrome: Symptoms, Vision, and Treatment" (*1*), which was published in *EHP* as a Grand Rounds in Environmental Medicine article. Swinker and Burke state that "the use of VCS as a diagnostic test for PEAS (and subsequent treatment of PEAS with cholestyramine) is not supported by a careful examination of the existing evidence." Their letter, however, does not discuss the data presented for the five Grand Rounds cases; they mention only our Case 1, and that is in reference to the patient's participation in the Maryland study on exposure to waterways containing toxin-producing *Pfiesteria* (*2*). We agree that previous publications only associated a VCS deficit with *Pfiesteria*-inhabited estuary contact, not with active PEAS. The North Carolina study, which associated the VCS deficit with estuarine contact (*3,4*), was designed to investigate the potential for persistent, estuary-associated health effects (*5*). Unlike the Maryland study, which involved recent exposure to fish kills and active PEAS (*2*), members of the North Carolina estuary cohort had no recent fish-kill exposure and were not selected because of complaints of current health effects (*5*). The North Carolina study (*5*) attempted to use the Centers for Disease Control and Prevention (CDC) symptom-based case definition (*6*) to assess PEAS at remote times of fish kill or lesioned fish contact, times at which VCS data were unavailable (*5*). The Virginia study (*7*) verified the VCS deficit in people contacting estuaries inhabited by "*Pfiesteria*-like organisms," but reported no active PEAS cases. Neither the North Carolina nor the Virginia study reported the prevalence of current PEAS symptoms in the exposed or control populations (*5,7*). The Grand Rounds cases, therefore, represent the first reports of VCS data measured before and during active PEAS diagnosis and after successful treatment (*1*). The dramatic and concurrent variations in VCS with the presence and absence of symptoms suggested that VCS measurements are a useful adjunct to the PEAS case definition.

In the Grand Rounds article, we carefully described the PEAS diagnostic criteria, involving exposure potential, symptoms, and the lack of alternative explanations. We measured VCS in Cases 2–5 to assess its usefulness in aiding PEAS diagnosis and recovery monitoring (*1*). All cases became ill shortly after exposure to estuaries in which *Pfiesteria* was identified and after dead or lesioned fish were observed. The cases initially had depressed VCS and multiple symptoms, including many of those listed by the CDC in the PEAS case definition, as well as the others reported (*1*). All cases had no history of illness involving neurologic dysfunction, allergy, asthma, eosinophilia, or neurotoxicant exposure. Complete blood count, comprehensive metabolic profile, and pulmonary function test results were within normal parameters. The pattern of VCS recovery and symptom resolution promptly following initiation of cholestyramine (CSM) therapy seen in all cases was documented prospectively in Case 2 (a researcher). His fall in VCS and symptom onset occurred within 36 hr of exposure to a site where a fish kill occurred 2 days later, and with very low probability of exposure to nonestuarine-associated neurotoxicants. Collectively, the cases demonstrated similar, large VCS deficits in acute, chronic, and repeated-acquisition illness, and subsequent rapid return to normal VCS coincident with CSM treatment.

The lack of significant exposure to known solvents in the Grand Rounds cases and the VCS recovery with treatment strongly argued that neither the symptoms nor VCS deficits were caused by solvent exposure. Solvent-induced symptoms and deficits in VCS and neurobehavioral performance are persistent or permanent, having been measured long after cessation of solvent

exposure (*8–10*). We found no literature on recovery from solvent- or other toxicant-induced VCS deficits. Symptomatic patients with occupational solvent exposure and VCS deficits did not respond to CSM treatment (*11*). The concern of possible hydrogen sulfide exposure, mentioned by Swinker and Burke, is highly unlikely to be a causative factor for VCS deficits in watermen who work outdoors without occupational exposure to sources of H_2S, such as submerged, decaying sediments of marshes.

Our most recent data, presented at the CDC National Conference on *Pfiesteria* (*12*) and published in *EHP* (*13*), confirmed the observations reported in the Grand Rounds article (*1*) in a population of 77 patients with residential and/or recreational exposure to *Pfiesteria*-inhabited estuaries in Maryland (*13*). Relative to two control populations totaling 87 patients, one with residential and/or recreational exposure to marine waters and one with no exposure to any bodies of water, the estuary cohort showed significantly depressed VCS. Thirty-seven members of the estuary cohort met the CDC case definition for PEAS (*6*). The 60% loss of VCS in the PEAS cases accounted for the entire VCS difference between the estuary and combined-control cohorts. VCS recovered to control levels as symptoms resolved within 2 weeks of CSM treatment. Shoemaker (*13*) also presented results from an earlier small, double-blinded, placebo-controlled, crossover clinical trial that showed the efficacy of CSM treatment in PEAS and the lack of a placebo effect. He also presented data indicating that repeated testing does not alter VCS scores and that CSM has no effect on VCS in non-PEAS patients treated for hypercholesterolemia (*13*).

Swinker and Burke refer to neuropsychologic tests as the "'gold standard' for verifying PEAS." This is curious because neuropsychologic test deficits are nonspecific, and Swinker and Burke object to the use of VCS testing in PEAS diagnosis because VCS deficits are nonspecific. We think that all tests which objectively describe neurologic deficits in symptom-described illness may assist in diagnosis, particularly when preexposure data are available. Issues of neuropsychologic testing availability in rural areas, patients' willingness to spend 3–4 hr in testing, and individual diagnosis criteria must be confronted, however, before neuropsychologic tests can become a gold standard for practicing physicians. The VCS data presented in the Grand Rounds article (*1*) showed 40–90% fluctuations between wellness and illness that occurred within days in individual cases. The VCS test provided a rapid, inexpensive, and readily available objective indicator that was strongly associated with corresponding changes in symptoms. All VCS deficits were outside the range of our (unpublished) age-adjusted, normative data.

Neither the Maryland study (*2*), our Grand Rounds article (*1*), nor our recent paper (*13*) definitively attributed illness to *Pfiesteria*-toxin(s) exposure. Definitive attribution of PEAS causation to *Pfiesteria* toxin(s), if that is the case, must await the identification of the toxin or toxins produced by *Pfiesteria*, detection of the toxin(s) in ill patients, and the absence of the toxin(s) in recovered patients. Recent research by Kimm-Brinson et al. (*14*) reported that a partially isolated toxin from *Pfiesteria* is an agonist for the adenosine-5′-triphosphate P2X7 receptors found in the membranes of microglia and peripheral macrophages. Activation of P2X7 receptors triggers a proinflammatory cytokine response that could potentially account for the *Pfiesteria*-related effects observed in humans and wildlife. The hypothesis that direct *Pfiesteria*-toxin(s) effects, combined with downstream cytokine effects (in the absence of abnormalities in standard immunologic system test results), are the sources of symptoms in PEAS cases should be pursued.

We wish to address several other issues raised by Swinker and Burke. They are correct in quoting Hudnell (*3*) on the hotline-caller data from the North Carolina study. The VCS data "do not indicate that visual function was affected by exposure to North Carolina estuaries" (p. 19). Swinker and Burke did not mention, however, the potentially confounding factors concerning characteristics of the hotline callers and their control group that may be responsible for the lack of association. First, of the 11 hotline callers assessed, Swinker et al. (*15*) subsequently reported that only 6 were found to have "relevant fish or water exposure," that only 6 had "actual" exposure (pp. 129–130). Second, analyses done at Swinker's request suggested VCS "abnormality" in the six cases with "relevant" or "actual" exposure (Figure 1). In fact, their VCS was at or below the level of the occupational estuary cohort (*3,4*) at all spatial frequencies. Swinker et al. (*15*) reported that only these six cases with actual exposure met the CDC criteria for estuary-associated syndrome, and that four had neuropsychologic impairment. They dismissed the diagnoses of estuary-associated syndrome, saying that "All six exposed cases had underlying or pre-existing medical condition(s) that could explain at least some of their symptoms" (*15*).

We submit that the description "could explain at least some of their symptoms" is insufficient for dismissing the diagnosis in situations where the VCS deficit is present and CSM treatment would clarify the issue. Third, the four callers without actual exposure, for whom VCS could be assessed, showed "normal" values (Figure 1)—values similar to those of the control offshore cohort (*3,4*). Fourth, VCS appeared to be "abnormal" in the hotline-caller control cohort (Figure 1). Of the 10 controls for whom VCS could be assessed, all reported exposures to North Carolina estuaries (recreational, $n = 10$; occupational, $n = 3$; living by the estuaries, $n = 2$), and 8 reported solvent exposure (occupational, $n = 5$; avocational, $n = 4$). Comparison of the VCS data for the entire hotline-caller cohort with that of the hotline-caller control cohort (*3*), therefore, did not give evidence of an estuary-associated VCS deficit in the callers, perhaps due to a confounding of relevant exposures between groups.

Swinker and Burke note that the CDC (*16*) did not receive reports of any verified cases of PEAS through 2000 but that "the health departments can facilitate the full

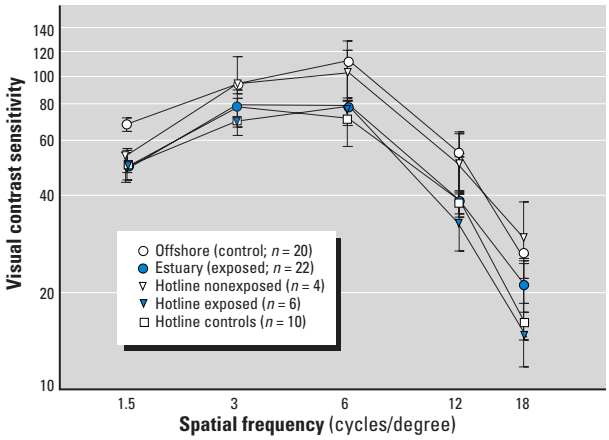

Figure 1. VCS functions (mean ± SEM) for five groups. The VCS deficit in the potentially exposed estuary cohort, statistically significant relative to the offshore cohort, was previously published (*3,4*) and is shown as a reference for the other groups. The VCS function for the nonexposed hotline callers (callers with no "actual" or "relevant" exposure as defined by Swinker) is similar to that of the unexposed offshore cohort, whereas the VCS values of the exposed hotline callers (callers with "actual" or "relevant" exposure as defined by Swinker) are at or below those of the estuary cohort at each spatial frequency. The VCS function for the hotline controls, who reported confounding estuary ($n = 10$) and solvent ($n = 8$) exposures, is similar to that of the estuary cohort. Estuary exposure, therefore, was associated with low VCS scores in the estuary cohort, the exposed hotline callers, and the hotline controls.

evaluation of cases." The State of Maryland Pfiesteria Surveillance Team announced that it had identified five patients meeting the CDC PEAS criteria from 1997 to 2000 (*17*). We commend the Maryland team and hope that our publications on PEAS will assist other health-care professionals in identifying PEAS cases.

Swinker and Burke omitted the quotation marks around "asymptomatic" in an e-mail message written by Shoemaker (*18*), which referred to patients with arthritic and biotoxic symptoms following dosages of the Lyme vaccine. The point Shoemaker made was that among patients who wanted the Lymerix vaccine following treatment with antibiotics for Lyme disease, there were many who had persistent symptoms attributed, perhaps inappropriately, to other illnesses. Shoemaker's data suggest that the persistent symptoms may represent another biotoxin-induced illness, post-Lyme syndrome. The patients' history of Lyme disease, the persistence of symptoms following substantial antibiotic treatment, the continued presence of a VCS deficit, and VCS recovery concurrent with symptom resolution after CSM treatment suggest that the bacteria may have released toxins before and/or during cell lysis. Patients inappropriately labeled as "cured" or "asymptomatic" are at a significant risk, in Shoemaker's opinion, of possible adverse effects from the Lymerix vaccine due to potentiation of a proinflammatory cytokine response. An accurate quote of the full sentence does not suggest that truly asymptomatic patients have a VCS deficit (*18*), as Swinker and Burke imply. If VCS deficits were as common as they imply, then it is unlikely that VCS testing would have been so successful in distinguishing toxin-affected or clinical groups from normal [see references in Shoemaker (*13*)].

Swinker and Burke indirectly criticize Shoemaker's Web site (*19*), which is still under construction. We thank them for pointing out typographical errors and regret that we have not yet had the time to complete manuscripts that will present data suggesting that the paradigm of chronic biotoxin-mediated illness may generalize to a number of conditions involving toxin-forming organisms. These organisms are increasingly being viewed as potential human health risks following direct contact or through contamination of food, water, and/or air. Because the Grand Rounds article (*1*) is early in the course of presentations on the basic concepts on biotoxin-mediated illnesses, there must be discussion and scientific debate regarding our observations. We agree with Swinker and Burke that our results must be confirmed in peer-reviewed publications. The purpose of the Grand Rounds article (*1*), our recent article (*13*), and the Web site was to introduce a series of new concepts to the academic community, primary-care physicians, and patients as part of a teaching and research-promoting process. Corrections and modifications will be made to the Web site as time and resources allow.

In their letter, Swinker and Burke refer to an advertisement for Shoemaker's book, *Desperation Medicine* (*20*). Cases supporting the hypothesis of generalization of a PEAS-like illness to patients with exposure to a variety of other biotoxin-producing organisms are described in *Desperation Medicine* (*20*). The book describes how symptoms in biotoxin-exposed patients stem from multiple system involvement, with day-to-day variation; there are no days in which affected patients are free from all symptoms. Taken alone, each symptom is nondiagnostic. Taken as a whole, however, as presented in the Grand Rounds article (*1*), the symptom complexes in patients who have particular environmental exposures and a distinct deficit in VCS are an important component in developing standard-of-care guidelines for the treating physician who must attempt diagnosis. The physician must take complete medical and potential biotoxin exposure histories and thoroughly characterize the patient's symptom profile, not relying on volunteered self-reports or a simple check-list. The physician may then identify the environmental exposure(s) associated with the illness, as well as those that are not, document the presence or absence of confounding neurotoxin exposures, administer clinical and laboratory tests of potentially confounding factors, and properly measure VCS to determine whether there is a deficit that is greatest at the mid-spatial frequencies. When clinical criteria for the likely presence of a biotoxin-mediated illness are met, prompt and predictable resolution of the symptom complex and VCS recovery, coincident with initiation of CSM treatment according to protocol, supports the diagnosis of chronic biotoxin-mediated illness. The usefulness of our case definition is particularly well demonstrated in patients with chronic illness that is unresponsive to previous treatments. We hope that acutely and chronically ill patients of all physicians will benefit from our new approach to diagnosing and treating the emerging health risk of biotoxin-induced illness.

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