Debating the Cause of a Neurological Disorder

IN HIS ARTICLE “GUAM’S DEADLY STALKER: ON THE LOOSE WORLDWIDE?” (NEWS FOCUS, 28 JULY, p. 428), G. Miller presents an objective review of Cox’s reformulated cycad hypothesis (1). This hypothesis suggests that ALS-PDC, a neurological disorder once common in the Chamorro people of Guam, is caused by eating fruit bats, who have a toxin, β-methylamino-L-alanine (BMAA), in their bodies from ingesting cycad seeds. However, the case is even less compelling than Miller suggests.

1) BMAA is present in Guamanian cycad seeds (2), but it is not very neurotoxic, as determined in primate studies. Spencer et al. administered “huge” doses (greater than 100 mg kg⁻¹ day for ~12 weeks), but they found no evidence of delayed or progressive neurodegeneration, two essential requirements for a toxin to fit the epidemiological data (3).

2) Banack and Cox report finding BMAA in the tissue of flying foxes collected on Guam, but they show no representative data (4). The selectivity of their assay is questionable and their mass analysis data are flawed. Determinations made on the dried skins of three museum specimens collected 50 years prior are of questionable relevance and are likely an artifact. It is dubious to assume that the BMAA is evenly distributed throughout the animal and that the highest value measured in the dried flesh can be multiplied by the average weight of a bat to yield the ingested dose.

3) Cox and colleagues say that they found BMAA in fixed (paraformaldehyde and sucrose) brain tissue collected from affected Guamanians and stored for years prior to analysis (5). Such storage would promote pronounced chemical change and these findings are likely an artifact. Notably, Montine et al. (6) found no evidence of BMAA in flash-frozen brain tissue obtained from Caucasians on the U.S. mainland nor Chamorros on Guam, regardless of the presence or absence of neurological disease.

4) There is little evidence that fruit bats were a major dietary component on Guam, and there are no reports of their consumption in either of the two other regions of high ALS-PDC incidence: Japan and west New Guinea.

The scientific community has been very receptive to the BMAA hypothesis; more than every, the onus is now on its proponents to provide compelling and credible data.

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The primary evidence for top-down effects was correlations interpreted by Halpern et al. as showing that spiny lobsters and Kellet’s whelks were “significantly important species, likely due to their strong impacts on key grazers of kelp (urchins) and algae (limpets and snails).” There is indirect evidence that lobsters may affect urchins (11, 12), but Kellet’s whelk is primarily a scavenger (13) whose abundance has been negatively correlated with kelp forests (14). Neither animal has been shown to have “strong” impacts on their prey species in California kelp forests. Halpern et al. could think of no mechanism by which the two other significant species “control” algae. The diets of these fish indicate no such mechanism; the correlations likely result from habitat preferences (15). The lack of significant correlation between kelp and urchins is counter to their hypothesis but was not discussed. The analytical results may be generally misleading due to weak trophic links [e.g.,
many of the grazers eat other algae in addition to kelp, and commonly eat drift, not attached plants (3)]. Thus, neither bottom-up nor top-down effects were tested and the conclusions, therefore, are unsubstantiated.

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References

IN THEIR REPORT “STRONG TOP-DOWN CONTROL in southern California kelp forest ecosystems” (26 May, p. 1230), B. S. Halpern et al. conclude that top-down (predatory) effects are strong and more important than bottom-up (nutrient) effects in setting kelp forest community structure. They reach this conclusion through a statistical technique that examines mathematical associations among variables. Like any statistical technique that tests for correlations, it is unable to assign causality or deal effectively with highly correlated explanatory variables (“multicolinearity”). By including several highly intercorrelated predictor variables in their statistical model, it is essentially impossible to estimate bottom-up effects (1,2). For example, because nutrient concentrations are tightly correlated with water temperature in southern California (3), it is probably impossible to separate temperature from bottom-up effects. Furthermore, their exclusion of sites from the warmest and most nutrient-poor waters (4) limits the ability to detect bottom-up effects.

Statistical associations between predator abundance and aspects of community structure lead Halpern and colleagues to conclude that predators drive community mechanisms. A more likely causal link, bottom-up effects driving kelp forest community structure (including predator abundance) (5–7), would produce identical statistical results. For example, the predatory kelp rockfish was identified as exerting significant “top-down control,” but this fish is found almost exclusively with kelp because it is dependent on it, not vice versa (7).

Finally, the purported top-down effects are weak, explaining at most 20% of the variation in community structure. Other variables (e.g., water temperature and geographic location) explained 2 to 27 times more of the variation in community structure for all trophic levels but kelps (4). Modern statistical tests give us unprecedented ability to discover patterns in complex data sets, but such patterns can only be interpreted when combined with a sound understanding of the natural history of the system.

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References

Response
FOSTER ET AL. AND STEELE ET AL. RAISE A number of concerns about our recent study. An important aspect of our analyses is that our dependent variables were species abundances, not the aggregate trophic values that are traditionally used. Our approach enhances the possibility of detecting either bottom-up or top-down patterns for individual or groups of species because assumptions about the nature (direct or indirect) of the relationships between species and trophic levels are unnecessary, and because it can detect compensatory dynamics within a trophic level that could eliminate aggregate top-down or bottom-up effects. Foster et al.’s concern about the species highlighted by our analyses likely arises from their expectation that direct trophic links must exist for the results to be valid. We were not assessing whether a “trophic cascade” existed, but instead evaluating the direction of control within communities. Indeed, our results may not have emerged from traditional approaches, and they highlight the potential importance of indirect effects in controlling community structure.

Both Letters express concern that we suggest cause and effect through correlations and not experiments. Despite reliance on correlational relationships, large-scale studies like ours have a long record of providing new insight through analysis over spatial and temporal scales beyond the reach and budget of experimental study. We focused on the hypothesized mechanisms that would be responsible for either bottom-up or top-down control—nutrient availability and predator abundance—and then determined the amount of variation explained by these two different groups of variables for algal and mid-trophic level abundances. The expected cause and effect are certainly implicit in our study, but will require significant resources before they can be tested experimentally.

Steele et al. are correct in noting that multicolinearity can create problems (1). However, our principal objective was to construct the best predictive model for both top-down and bottom-up variables, a situation in which “multicolinearity can be effectively ignored” [(1), p. 2811]. Nevertheless, we limited multicolinearity problems within each different predictor group by eliminating highly multicollinear variables, an approach (1) that acts conservatively to decrease significant results (top-down control, in our case). Furthermore, we reported “pure” top-down and bottom-up effects in table S2 and Fig. 3, which are the amounts of explained variation after eliminating the multicolinearities between the different predictor groups. Contrary to Steele et al.’s expectations, top-down and spatial or temperature variables were colinear while bottom-up and temperature variables were not (see table), such that adding multicolinearity to our results would have suggested even stronger top-down effects.
In addition, the results from our cited companion paper (2) show that the combination of wave disturbance and El Niño–Southern Oscillation (ENSO) explains only 6% of the variance, and in situ temperature explains less than 1% of the variance in kelp forest community structure based on 18 years of data spanning several strong and weak ENSO events. As we noted (see SOM), the use of satellite-derived productivity data in coastal waters has been extensively validated in our study region [(see also (3)]. Importantly, the variance in primary production (4) is sufficient to detect potential bottom-up effects, despite missing the extreme nutrient limitation encountered at the southern limit of *M. pyrifera*.

Other variables such as geographic location are, indeed, at least as important as the top-down variables we identified (2). However, explaining 20% of variation in community structure is a notable result (5), and these “other” variables are largely outside the human influence and so less useful for management purposes.

The claim that our results run counter to the literature on kelp forest ecology is untrue [see, for example, (6–9)], and we disagree with the suggestion that bottom-up effects offer a more parsimonious explanation of our results. Also, the referenced bottom-up associations are not tests of nutrient versus predation effects on entire kelp forest communities and counter examples exist, as with the monitoring of extreme eutrophication of kelp forests off San Diego that found no effect on kelp forest communities (10). Consequently, compensatory mechanisms among species are likely more important than a simple trophic cascade framework would suggest, with these effects driven by top-down forces. Our novel approach allowed us to uncover these results and to open up the quest for the mechanisms driving them.

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**CORRECTIONS AND CLARIFICATIONS**

Science Careers: "Young scientists need firm plan to make up for a late start" by K. Robinson (8 Sept., p. 1454). Several lines near the end of the article on page 1457 were dropped during production. The correct passage should read:

"Don’t assume that your 403(b) plan representative can help you. They may be trained in sales, not financial planning, and may not know, for instance, whether you have enough emergency cash set aside. You will be served best by an adviser who will consider not just investments but all aspects of your financial life.

Consumer advocates—including Consumers Union, the nonprofit publisher of Consumer Reports—recommend a ‘fee-only’ financial adviser: one who takes no commissions and is paid directly by the client."

**News of the Week:** "Genomes highlight plant pathogens’ powerful arsenal" by E. Stokstad (1 Sept., p. 1217). The photo credit should be "D. Schmidt, Garbelotto Laboratory, UC Berkeley."

**News Focus:** "One year after, New Orleans researchers struggle to rebuild" by J. Kaiser (25 Aug., p. 1038). The statement "New enrollment at Tulane’s medical school is down by about one-third" refers specifically to graduate students. First-year medical student enrollment is 165 this year, 10 more than in previous years.

**Policy Forum:** "Public acceptance of evolution" by J. D. Miller (1 Aug., p. 763). The URL for the Supporting Online Material is incorrect. It should be www.sciencemag.org/content/full/313/5788/765/DC1. The link has been corrected in the online version.

**Reports:** "Permanent El Niño–like conditions during the Pliocene warm period" by M. W. Arau et al. (29 July 2005, p. 758). In references 7, 9, and 10, the first author should be D.-Z. Sun, not D.-E. Sun.

**TECHNICAL COMMENT ABSTRACTS**

**Comment on “A Keystone Mutualism Drives Pattern in a Power Function”**

David Alonso and Mercedes Pascual

Vandermeer and Perfecto (Reports, 17 February 2006, p. 1000) reported a general power law pattern in the distribution of a common agricultural pest. However, there is an exact analytical solution for the expected cluster distribution under the proposed null model of density-independent growth in a patchy landscape. Reanalysis of the data shows that the system is not in a critical state but confirms the importance of a mutualism.

Full text at www.sciencemag.org/cgi/content/full/313/5794/1739

**Comment on “A Keystone Mutualism Drives Pattern in a Power Function”**

Salvador Pueyo and Roger Jovani

Vandermeer and Perfecto (Reports, 17 February 2006, p. 1000) maintain that a mutualist ant disrupts the power law distribution of scale insect abundances. However, reanalysis of the data reveals that ants cause an increase in the range of the power law and modify its exponent. We present a tentative, but more realistic, model that is suitable for quantitative predictions.

Full text at www.sciencemag.org/cgi/content/full/313/5794/1739

**Response to Comments on “A Keystone Mutualism Drives Pattern in a Power Function”**

John Vandermeer and Ivette Perfecto

The comments by Alonso and Pascual and by Pueyo and Jovani clarify the power law distribution of subpopulations of the scale insect *Coccus viridis*. The low density deviations are now seen as part of a negative binomial distribution and the high density deviations as resulting from a change in the parameters of the power law. Our biological conclusion that an ant mutualism modifies the form of the power law is thus strengthened.

Full text at www.sciencemag.org/cgi/content/full/313/5794/1739

**Letters to the Editor**

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.