Beleaguering the Cancer Establishment

Vitamin C and Cancer. Medicine or Politics? EVELLEEN RICHARDS. St. Martin's Press, New York, 1991. xiv, 269 pp. $35.

The author's aim with this book is twofold: to provide a case study of "social construction of science," in line with a current trend in science studies; and to take a swing at the medical establishment, in which regard she steps forth, in the book's final chapter, as an outright spokesperson for alternative medicine.

Richards's strategy is to question the key procedure in the testing of new cancer drugs: the randomized controlled clinical trial. If she can show that there can be no agreement based on factual evidence among proponents and opponents of new therapies, her case would fit right in with the claims of those who see controversies in science as merely a matter of scientists' social or strategic interests, disregarding intellectual commitments, convictions about "good science," standards of proof, and the like. Moreover, the failure of the randomized controlled clinical trial to determine the therapeutic efficacy of new experimental drugs, or of any drug, would serve to undermine the medical experts' monopoly on treatment of cancer patients and open up the possibility for patients to choose freely among therapies, including "alternative" ones.

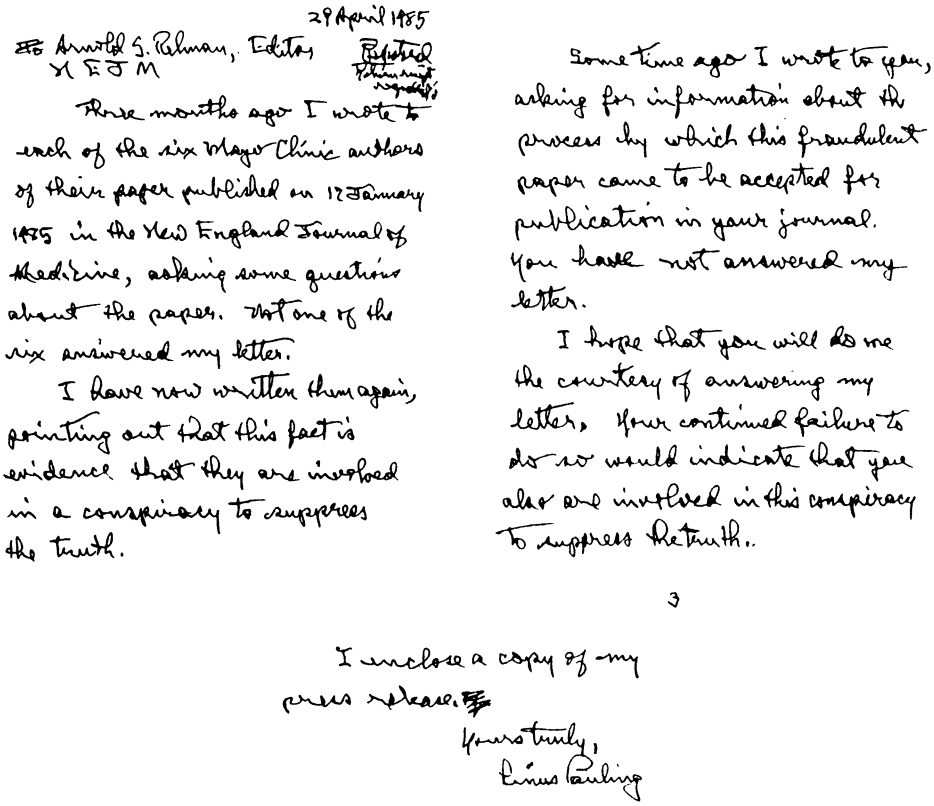
Richards's choice of case study, Linus Pauling and his fight to get vitamin C accepted as a treatment for cancer, may not quite lend itself to such ambitious aims. The reader who wishes to assess just how well Richards in fact succeeds in proving her point is in for some serious work. *Vitamin C and Cancer* is an exceedingly well documented, quite complicated case study in which it is sometimes hard to keep track of the sequence and significance of events, despite the author's cross-referencing efforts.

Luckily, the book does not have to be read in such an inquisitory spirit. The case study on its own provides interesting reading and fascinating insights into the world of science and medicine. In fact, the book can be read in several different ways. One can see Pauling as a folk hero, bravely fighting the medical establishment for a fair test of his alternative, easily accessible, and potentially beneficial megavitamin cancer therapy. One can see him as the *enfant terrible* of established science and medicine, through his various actions testing and challenging the hidden assumptions of established rules and procedures. Or the book might be read as a handbook in scientific Machiavellianism.

The book describes the long-term (about 20 years) collaboration between Pauling and a Scottish doctor, Ewan Cameron, both champions of vitamin C therapy for cancer, albeit with initially rather different rationales. Cameron had written a book on his theoretical views of the cancer process in 1966, explaining the spread of cancer as having to do with the failure of the inhibitor (PHI) of the enzyme hyaluronidase to stop overproduction of the enzyme. This led to the weakening of the "ground substance" surrounding the cells. Cameron believed ascorbic acid to be structurally similar to PHI and speculated that vitamin C may help the body synthesize needed PHI and thus control cancer. He claimed some good observational results from his hospital.

Interestingly, according to Richards, Pauling's preoccupation with vitamin C is no mere whim: it is quite consistent with his overall structural molecular perspective. In fact, his idea of "orthomolecular" medicine stems from one of his many scientific feats, his discovery that sickle cell anemia is due to a faulty inherited molecular structure. According to Pauling, humans suffer from a genetic disease of vitamin C deficiency that has to be compensated for with daily megadoses (this he first argued in conjunction with the common cold). He also ascribed antiviral properties and ground-substance–strengthening properties to vitamin C. Neither Pauling nor Cameron claimed to have found a cure for cancer, but they were convinced of vitamin C's ability to significantly improve and prolong the lives of cancer patients.

Double-blind experimental testing is the way to persuade the U.S. medical establishment about the efficacy of new drugs. As the Pauling story develops, Pauling is in principle interested in securing such a testing of vitamin C. This is to be preceded by



29 April 1985

Arnold S. Relman, Editor
NEJM

Rejected
Plagiarism
suspected

Some months ago I wrote to each of the six Mayo Clinic authors of their paper published on 17 January 1985 in the New England Journal of Medicine, asking some questions about the paper. Not one of the six answered my letter.

I have now written them again, pointing out that this fact is evidence that they are involved in a conspiracy to suppress the truth.

Some time ago I wrote to you, asking for information about the process by which this fraudulent paper came to be accepted for publication in your journal. You have not answered my letter.

I hope that you will do me the courtesy of answering my letter. Your continued failure to do so would indicate that you also are involved in this conspiracy to suppress the truth.

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I enclose a copy of my press release.

Yours truly,
Linus Pauling

"The original draft of Linus Pauling's letter to Arnold Relman, editor of the *New England Journal of Medicine*, in the wake of the second Mayo Clinic trial of vitamin C." [Reproduced in *Vitamin C and Cancer* by permission of Linus Pauling]

animal studies, which in Pauling's case present various problems, not the least monetary ones. Meanwhile, he is trying to use his considerable scientific and political clout to get his own and Cameron's claims published in scientific or medical journals. There is much instructive detail in the letter exchanges of these two, discussing strategies and revisions in order to make their publications palatable to various fora. There are also the maneuvers of journal editors who find themselves in novel situations—among them an editor of the *Proceedings of the National Academy of Science* who risks being accused of advocating vitamin C therapy if he publishes Pauling's article or of changing the publication rules if he doesn't. (He didn't.)

By pulling various strings, Pauling succeeds in getting the vitamin C therapy tested in a double-blind study, conducted by Charles Moertel at the Mayo Clinic, the results of which are published in the *New England Journal of Medicine*. The results are negative. Pauling protests, pointing to faults in the design (for vitamin C therapy to work, patients should not have been given toxic drugs before). Unbelievably, Pauling's energy, networking skills, and considerable prestige (as a winner of two Nobel prizes) furnish him with a chance to have his and Cameron's claims tested once more, again at the Mayo clinic, this time with patients who have not been given cytotoxic drugs. But even this double-blind experiment shows zero results. Pauling finds serious faults also with this retrial, again published in the *New England Journal of Medicine*, and writes rebuttals and appeals for one more trial, suggesting a procedure by which there would be careful controls, longer assessment times, and minutely agreed-upon details in a collaborative effort between Moertel's team and his own. But by now both Moertel and the editor consider the case closed. Pauling is not even allowed to publish his rebuttal.

What does this story prove? According to Richards, the treatment of Pauling and Cameron is an example of the medical establishment not tolerating alternative (over-the-counter and cheap) drugs, since the doctors want to be in control of cancer patients. To boost her case, she compares the vitamin C case to the medical establishment's attitude to 5-fluorouracil, a cytotoxic drug, and to interferon, a supposed wonder drug. Fluorouracil, being a cell-killing agent, fits well with the medical conception of a war against invading cancer cells. But why is it, Richards asks, that despite admittedly questionable benefits of this drug for terminal cancer patients, fluorouracil continues to be used? She does not buy Moertel's own explanation that one has to give patients "hope." And why is it that interferon, after turning out not really to live up to its promise, is still championed as an anticancer agent by the medical community? Richards suggests that this is because it is supposedly compatible with the cytotoxic drugs used in conventional cancer therapy, not incompatible like vitamin C, and also because it is quite expensive and can be administered only by experts. Her conclusion is that what fits in with established practice will be considered but what doesn't won't, since the main interest of the medical doctors is in defending their professional authority as experts.

Richards does not raise the possibility that the medical doctors might have good *scientific* reasons for the championing of fluorouracil and interferon, but not vitamin C. An alternative way of looking at the situation would be to see it as a basic opposition between two ways of thinking about cancer: Pauling's and Cameron's "old fashioned" structural/orthomolecular or enzymatic views, and the "modern" DNA orientation of current medical research. In this light the continuing reliance on drugs acting on the cell nucleus (fluorouracil or interferon), despite their limited therapeutic power, appears quite logical. This could be seen as illustrating the medical researchers' profound conviction that the answer to cancer has ultimately to be found in the cell nucleus. It is also understandable that Pauling and Cameron's claims, positing a hypothetical mechanism while yielding no spectacular results, could be of little interest to the cancer establishment, particularly since the administration of vitamin C megadoses would require the absence of cytotoxic drugs. Richards mentions all this, but for her the question is not of cognitive commitments or frameworks of research, but ultimately of expert power.

Richards briefly touches on the ethical problem with double-blind experiments for experimental drugs in the case of cancer: the withholding of a potentially useful experimental drug from the control group while the research is going on. Her reason for rejecting the idea of controlled clinical trials in medicine seems to be epistemological rather than ethical, however; she uses the Pauling-Cameron case to demonstrate how no agreement about testing procedures and results can be possible and therefore the whole process "must" be a political struggle. It is interesting that at least Pauling and Cameron themselves thought the dispute could be settled, and obviously there were no *logical* obstacles to an agreement about the conditions of a fair testing procedure, with an emphasis on correcting earlier mistakes. It just turned out that no such third trial came about.

Scientific and medical research operates in real time with real people. There are only limited resources of time and money available. The ultimate results are never in; instead researchers have to work with plausibility scenarios, intuition, rules of thumb, and the like. In my view, the medical researchers were justified in stopping paying attention to Pauling's claims after two trials, particularly since his scenario was anyway not one for finding the definitive cure for cancer, which was what the researchers were interested in. Experience shows that in order to be persuasive in science, you have to demonstrate a mechanism for the effect claimed, or at least present an obvious result. Not even obvious results are always enough, as the story of Semmelweiss, who, on the eve of Lister's discovery of antisepsis and Pasteur's germ theory, was not able to convince his colleagues that washing of hands with carbolic acid would prevent women from dying in childbirth at his hospital, reminds us.

But as an example of the fact that clear effects can indeed persuade the medical establishment one may mention aspirin, an over-the-counter drug if there ever was one—and one whose mechanism of action was not known until recently. Low-dose aspirin intake is now believed to diminish the risk of heart disease. Ironically, as I am reviewing *Vitamin C and Cancer*, a book advocating the demise of double-blind clinical trials, I come across a reference to the 30 November 1991 issue of *The Lancet*, where the first large-scale placebo-controlled study of the effects of low-dose aspirin in stroke prevention has been published. According to this study, taking aspirin reduces stroke victims' risk of a second stroke or fatal heart attack by 18 percent.

Whether or not one buys into Richards's general framework, what might one conclude about the case of vitamin C and cancer? In my view, Richards's book contributes to keeping the possibility alive that there may indeed be something to Pauling's and Cameron's (relatively moderate) claims, even though the case may have appeared closed—as it surely must have to many members of the scientific and medical establishment—in 1985, after the second Mayo trial. But was the case really closed? Not according to Pauling. Richards gives the last word to this indomitable spirit. In 1989, almost 90 years old, Pauling, together with an associate, published a paper in *PNAS* in which he set out to demonstrate

that the second Mayo trial was flawed, this time on biostatistical grounds. Pauling also succeeded in presenting his case to the new director of the National Cancer Institute, the funding power behind the two Mayo trials. It seems that Pauling in this director found a sympathetic ear and got some advice on how best to proceed in medically proving his case. A standard clinical trial was not suggested. The randomized controlled clinical trial, typically looking for relatively short-term and dramatic improvements, may not after all be the most suitable scientific method for assessing the efficacy of agents with moderate and long-term fortifying effects. A reconsideration of the standards of proof in medical research could turn out to be the most important outcome of the prolonged controversy about vitamin C and cancer.

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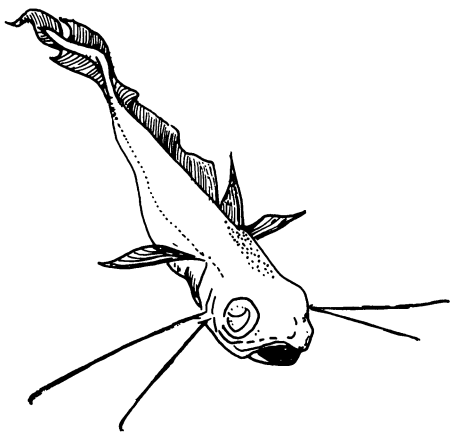
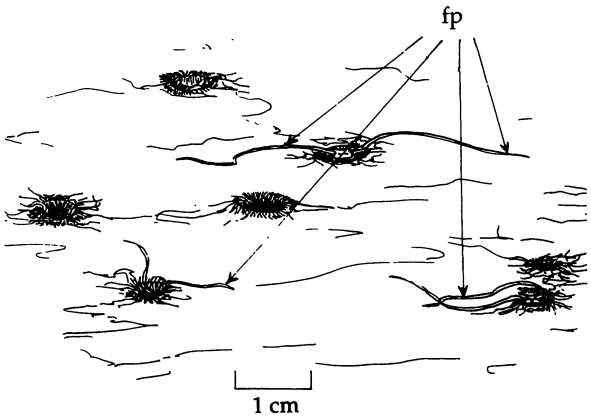
Life in the Abyss

Deep-Sea Biology. A Natural History of Organisms at the Deep-Sea Floor. JOHN D. GAGE and PAUL A. TYLER. Cambridge University Press, New York, 1991. xvi, 504 pp., illus. $135.

Sunlight at noon turns quickly to dusk as you descend beneath the surface of the open ocean. Continue your descent to the abyssal seafloor in the blackness of midnight, lit only by splashes of luminescent light as planktonic organisms are disturbed by your path through the water. Once on the bottom even your brightest lights won't penetrate very far. But under their spotlight you will find illuminated a minute patch of the largest, most inaccessible, and least understood ecosystem on our planet. You will see a world that is often more like the stage set of a science-fiction movie than anything familiar to most of us. You are likely to encounter fantastic creatures, like single-celled protozoans of grapefruit proportions, or giant stalk-borne tunicates looking like paper grocery sacks on sticks, or herds of sea cucumbers congregating on the tan muds of soft-sediment plains.



"Deep-sea morid fish probing the ooze for food with its long, sensitive pelvic fin rays." Some 50 species of deep-sea Moridae (cods) are known. . . . They often possess an elaborate light-producing organ . . . containing symbiotic luminous bacteria." [From *Deep-Sea Biology*; redrawn from B. C. Heezen and C. D. Hollister, *The Face of the Deep*, 1971]



"Surface-deposit feeding by the shallow-water, mud dwelling spionid *Malacoceros*; the paired, ciliated feeding palps (fp) select particles as they explore the sediment surface. . . . Deep-sea spionids probably feed in a similar manner, although they will rarely live at such high density as depicted; this foraging strategy becoming increasingly unable to provide resources at a rate sufficient to meet metabolic demands as food supplies become more sparse with increasing depth and distance from land." [From *Deep-Sea Biology*; drawing courtesy T. H. Pearson, SEAS Ltd., Oban]

Over the past 25 years there has been a major evolution in our thoughts about the nature of the abyssal seafloor environment. From a perception of the deep sea as a biologically sterile, spatially homogeneous, and temporally unchanging environment, we have come to know that life on the seafloor can in some places be abundant, sometimes spectacularly so. The diversity of the fauna of cold abyssal muds can be remarkably high, with species richness rivaling that of tropical rain forests. Spatial heterogeneity can be an important control of patterns in species abundance and diversity at centimeter, meter, and kilometer scales. And seasonal fluxes of phytodetritus to the seafloor provide the bass beat for the reproductive tempo of abyssal life in many regions.

Population genetics and molecular techniques are opening doors to an understanding of speciation and zoogeographic processes in the deep sea. Some of what were once believed to be cosmopolitan species are now appreciated as suites of multiple species, isolated by "invisible" barriers. Identifying these barriers challenges the imagination and entices even the novice into stimulating speculation. Like mountain ranges in terrestrial systems, are mid-ocean ridges that girdle the globe effective barriers to dispersal? What more subtle barriers might exist?

Advances in biochemical techniques are revealing surprising details about the life histories of many species. An intriguing strategy has been described in some mollusk species whose larvae leave the abyssopelagic realm entirely, ascending to near-surface waters where they feed and then descending back to the abyss to metamorphose and mature.

Of course, the event of the century in deep-sea biology was the discovery of hydrothermal vents at seafloor spreading centers where entire communities are fueled not by sunlight and photosynthesis but by geothermal processes and chemosynthesis. Symbioses between chemoautotrophic bacteria and invertebrate hosts dominate the biomass of most of these communities. Intensive investigations on the nature of hydrothermal vent communities have raised fundamental issues, including the role deep-sea vents played in the origin of life and as biotic refuges from the catastrophic extinctions that occurred in terrestrial and shallow-water environments, the thermal extremes at which life can exist, and the consequences of a geothermal source of light on the seafloor.

Deep-Sea Biology is a scholarly celebration of the growth of our knowledge about biological systems on the seafloor. Gage and Tyler initially engage us in a review of the natural history of deep-sea benthic organisms and proceed from there into discussions of patterns and rates and processes in space and time. Research of the past decade and a half is placed in its historical context, and many of the gaps in the depth and breadth of our understanding of the biology of the deep-sea are identified. The volume closes with a chapter that underscores the links between the seafloor environment, the world ocean, and world climate and provides a cautionary note to plans for exploitation of a great wilderness area still poorly understood and in many places still totally unexplored.

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