Vitamin C Gets a Little Respect

Some researchers say the climate in this controversial field is changing as data mount on the role of antioxidants in disease and health. Others remain skeptical

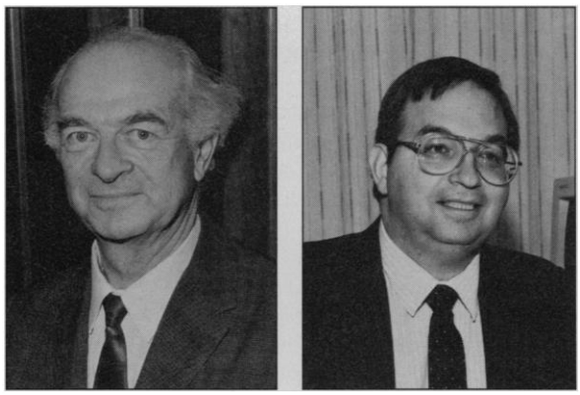
RESEARCHERS WHO WORK ON VITAMIN C have something in common with comedian Rodney Dangerfield: They don't get much respect. At least they haven't until lately. Vitamin C (ascorbic acid) has for more than two decades been inextricably associated in the minds of the public and of many researchers with the controversial claims of Linus Pauling, the world-renowned Nobel laureate chemist who argues that megadoses of the stuff can cure everything from the common cold to cancer. Nobel Prize or not, claims like those would make any cautious researcher run for cover. And they have. But now there are signs that vitamin C research may be approaching a turning point. As more researchers begin looking into the chemical's potential for preventing or curing disease, some say that the field is shedding its embarrassing past and achieving the respectability it has long been groping for.

"There is no question that the status of vitamin C has changed in a lot of researchers' minds," says epidemiologist Gladys Block, who recently moved from the National Cancer Institute (NCI) to the School of Public Health at the University of California, Berkeley. Block points to a growing body of information about the role antioxidants—including vitamin C—may play in chronic diseases such as cancer, heart disease, even AIDS, and an increased interest in vitamin C research on the part of the National Institutes of Health. Indeed, just last month the National Heart, Lung, and Blood Institute (NHLBI) devoted a workshop to antioxidants and heart disease. And that workshop followed a first-ever conference on vitamin C held in September 1990 by the NCI.

But those few signs don't guarantee that vitamin C research will fully live down its checkered past. The jury is still out on whether there are enough new data to establish vitamin C as a respectable research subject, and there are still skeptics aplenty. "We're talking about speculations that have nothing to do with public health," says nutritionist Robert Olson of the State University of New York (SUNY) at Stony Brook, dismissing virtually all the results of vitamin C research. "Many of them are just old experiments wrapped in new packages."

But critics like Olson are "like the little Dutch boy with his finger in the dyke," says one vitamin C researcher who—perhaps tellingly—prefers anonymity. "This is a tide that can't be stopped."

Maybe so; the strength of this tide is obviously still a matter of opinion. But what's not open for debate is the fact that the chief challenge the field faces is overcoming the overwhelming hype of the past several decades. That hype derived from a simple but compelling logic that goes like this: Many of the things that are bad for us, such as cigarette smoke and smog, exert their damage through chemical oxidation of lipids, proteins, and DNA. Vitamin C is a good antioxidant, well-suited to reducing those nasty substances chemically before they can do their oxidative damage. And, since humans are among the few mammals that don't make vitamin C for themselves (and the substance is apparently nontoxic, even in large doses), why not play it safe and take a lot? Pauling, for example, advocates megadoses of 18 grams of vitamin C per day (300 times the recommended daily allowance), though he has produced no evidence for therapeutic benefit that is solid enough to convince other scientists.



Old breed and new wave. *Linus Pauling* (left); *Stuart Marcus works on vitamin C and cancer therapy toxicity.*

Pauling's best-known—and most controversial—study, in which he and Scottish physician Ewan Cameron attempted to demonstrate that vitamin C prolonged the lives of cancer patients, was widely criticized because it was not blinded, and the controls were cases chosen from historical records. Just this past year, an NCI-appointed panel reviewed Pauling's and Cameron's data and found them inconclusive.

Worse yet for Pauling's position, the evidence against him has been found by most researchers to be solid. A double-blind Canadian trial showed that vitamin C did not prevent colds, and two double-blind studies at the Mayo Clinic found no anticancer effects of vitamin C.

This has left Pauling enraged. He told *Science* that he considers the Mayo Clinic studies "fraudulent" because they claim to have disproven Cameron's results but didn't use his protocols and administered vitamin C for no longer than 75 days. But while Pauling has not accomplished his goal of getting the NCI to sponsor a clinical trial of vitamin C as a cancer treatment, he did manage last year to convince NCI director Samuel Broder to agree to hold a conference on vitamin C research.

How did he win over Broder? "We had to do something; we had really done nothing before," says NCI program officer Donald Earl Henson, whom Broder asked to organize the meeting. Henson adds that his goal was "to shift the hype from the public to the scientific arena." The meeting was intended to be low profile—but co-organizer Block complains it had almost no profile at all. The meeting was shunned by all the invited medical journals, with the exception of *JAMA*, and also by much of the NCI. "I sent invitations to basically every branch chief at the NCI," she says, "and essentially nobody came."

The muted response to the NCI conference may be because vitamin C and cancer—as contrasted with some other areas of vitamin C research—is one area in which little has changed. The fundamental fact—that "when you eat foods that are high in vitamin C, you have a lower risk of cancer," as Peter Greenwald, chief of the NCI division of prevention and control puts it—is considered to be well established. NCI has a number of cancer-prevention trials under way testing vitamin C and other antioxidant supplements, but results are not available. And no one

besides Pauling has been willing to touch the issue of vitamin C as an anticancer drug.

But, as the meeting demonstrated, there has been progress in other areas of vitamin C research. Henson, a self-described skeptic about vitamin C, says the meeting held some promising new surprises, including several studies suggesting that vitamin C may be useful in cancer treatment, not as a primary anticancer drug, but as a means of counteracting the toxicity of some cancer treatments. For example, Hiroshi Kan Shimpo, of Fujita Health University in Japan, has shown in animal studies that vitamin C blocks the oxidative damage to heart muscle that often occurs as a side effect of treatment with the powerful anticancer drug adriamycin. And Stuart Marcus, working with Peter Wiernik at the Montefiore Medical Center in New York, found that patients undergoing cancer treatment with interleukin-2 suffer a precipitous drop in vitamin C—to levels low enough to cause scurvy—that could contribute to the treatment's toxicity. Henson called the studies "one of the most exciting parts of the meeting. They need to be followed up."


Jane Scherr

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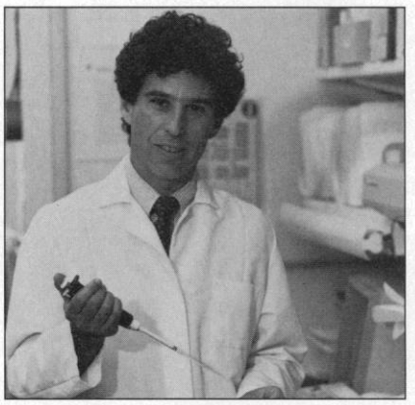

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Another potential role for vitamin C or other antioxidants that was presented at last year's meeting, and then served as the focus of last month's NHLBI workshop, is in the prevention of atherosclerosis. For 10 years, evidence has been building that oxidization of low-density lipoprotein (LDL) speeds the formation of atherosclerotic lesions. The most compelling evidence came in 1988, when Daniel Steinberg and his co-workers at the University of California, San Diego, showed that the antioxidant drug probucol could reduce atherosclerotic lesions in rabbits by 50%. At least two labs have shown that vitamin C may also protect against the process in humans. Balz Frei, now at the Harvard School of Public Health, working with Bruce Ames of UC Berkeley, and Kenny Jialal and Scott Grundy at the University of Texas Southwestern Medical Center, exposed human plasma to oxidative substances and found that vitamin C protects LDL from oxidation. "There was no oxidative damage [to LDL] as long as vitamin C was around," says Frei. Once the vitamin C naturally present in the plasma was used up, LDL oxidation began.

SUNY's Olson says such test-tube data have no relevance to what actually goes on in the body. But not all researchers share his view. At last month's heart institute workshop, which Steinberg organized to test the waters for a clinical trial, many of the participants concluded that the evidence is approaching the level needed to justify beginning clinical trials with antioxidants. The major question remaining, Steinberg says, is which antioxidants would be the best to try.

That puzzle is a recurring one in antioxidant research, since it's easy to assume that if one antioxidant produces results, others will as well. Yet "all antioxidants are not the same," warns Leonard Herzenberg of Stanford Medical School, who has been studying the effects of levels of the intracellular antioxidant glutathione on the progress of HIV infection. People with HIV have glutathione deficiencies, and Herzenberg's group, as well as a team including Anthony Fauci of NIH and Alton Meister of Cornell Medical College, found in cell-culture experiments that the drug N-acetyl-cysteine (NAC), which replenishes glutathione, slows HIV production, apparently by inhibiting viral transcription.

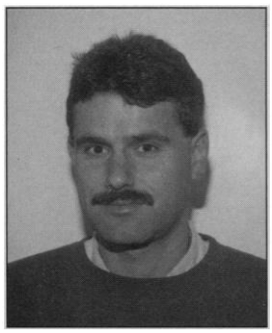
Raxit Jariwalla and Steve Harakeh of the Linus Pauling Institute in Palo Alto, California, have found that vitamin C also inhibits HIV infection of cultured cells, a result that might seem logical since both vitamin C and glutathione are water-soluble antioxidants. But Jariwalla sees no inhibition of HIV transcription in his experiments, suggesting that vitamin C is working through a different—and currently unknown—means.

Does either antioxidant show promise for treating AIDS? Jariwalla admits that he has heard of only one anecdotal case in which an AIDS patient claimed that megadoses of vitamin C improved quantitative clinical markers such as T-cell count. Whether any better can be said for NAC or other glutathione precursors may soon be known: Several clinical trials of NAC and other glutathione precursors in HIV-infected patients are currently under way at NIH, Stanford, and elsewhere.

Meister, whose work centers on the study of glutathione, agrees with Herzenberg that vitamin C may not substitute for glutathione in AIDS patients. But his group recently found one instance in which it seems to. Vitamin C, they found, can save newborn rats with drug-induced glutathione deficiency from otherwise certain death by multiple organ failure. "If you take away glutathione you have problems," says Meister, "and you can make up for some of those problems with ascorbate." But, he adds, "we have to go to literally Linus Pauling-recommended doses"—500 times the rat equivalent of the recommended daily allowance. Nevertheless, he suggests vitamin C therapy may be useful in the particular instance of children born with a rare defect in glutathione production.

Despite his clear enthusiasm about his findings, Meister is obviously wary about being labeled a vitamin C booster. And he is not alone. UC San Diego's Steinberg admits he felt "embarrassed" when he first started talking about his evidence that antioxidants may protect against atherosclerosis. "I would see people's eyes rolling up to the ceiling," he says. "I felt very awkward." Indeed, NCI's Greenwald says he believes that the fear of being marginalized may be keeping some researchers from studying vitamins and antioxidants. "Some scientists don't want to get too involved because there is a fringe group, and they don't want to be associated with that."

What the new breed of vitamin C researchers are attempting to do is dissociate themselves from that fringe. One researcher in the field thinks they're on the way to doing that—but they're not there yet. "There are some things that are new and exciting," says vitamin researcher Mark Levine of the National Institute of Diabetes, Digestive, and Kidney Diseases. But Levine adds that the field is still in a state of transition. A lot of low-quality work, left over from the old days, is still being done: poorly controlled experiments and physiological measurements of vitamin C levels that use outdated and unreliable assays. "The only way to get at vitamin C is to do the basic stuff that has never been properly done at all," Levine says, pointing out for starters that no one really knows for sure what blood levels you get from taking a gram of vitamin C, or 10 grams, or 20, leaving the meaning of megadoses completely unknown.



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Levine is gearing up to address the question of tissue levels of the vitamin using a newly developed and more reliable assay in human volunteers. Once tissue levels are known, Levine proposes to analyze vitamin C systematically, to deduce the optimum level for various functions in the body, using whole cell or organ preparations. "You have to go after this and ask these questions," says Levine. "You can't just assume that more is better." Levine's approach, which he has begun to apply in several tissues, has won praise from a variety of quarters, but not from old-time nutritionists like Olson. "He is doing all kinds of research in vitro, and claiming that it applies to the intact body, which is nonsense," Olson fumes.

It's not surprising that Levine's work calls forth sharply divided opinions. Almost everything about vitamin C still elicits much stronger reactions than most research subjects—reactions that can only be considered appropriate, given how recently the topic was far outside the mainstream of science. But, like many scientific ideas once thought to be absurd that later appear in the guise of orthodoxy, vitamin C seems to be creeping closer and closer to winning the respect that Rodney Dangerfield never quite seems to get. ■ MARCIA BARINAGA

Duesberg Vindicated? Not Yet

A surprising—some say shocking—result from an AIDS vaccine trial in monkeys has forced researchers to reconsider some of their approaches to developing an AIDS vaccine for humans. Writing in the 3 October issue of *Nature*, E. James Stott and his colleagues at the National Institute for Biological Standards and Control in Hertfordshire, England, found that a vaccine made from uninfected human T-cells—intended as a control—was at least as effective in protecting animals from infection with SIV (the simian version of the AIDS virus) as a vaccine that was made with the attenuated virus itself grown in the same T-cell line.

But if researchers are uncertain what to make of the new findings, they had a very different reaction to a *Nature* article (26 September, p. 297), written by the journal's editor John Maddox, about the implications of the research. Maddox concluded that Stott's study, together with results recently published in *Science* (6 September, p. 1138) suggesting that AIDS shares features with autoimmune diseases, supported the controversial thesis espoused by virologist Peter Duesberg: namely, that HIV is not the cause of AIDS.

"In general, I'm pretty mild mannered, and I was furious" about Maddox's article, says David D. Ho, director of the Aaron Diamond AIDS Research Center at the New York University School of Medicine. Ho isn't alone. Numerous other researchers contacted by *Science* failed to see any connection whatsoever between Stott's work or the *Science* study and the stand taken by Duesberg, who is a professor at the University of California at Berkeley. That goes for Duesberg, too: "Those studies have nothing to do with [my position]," he says.

What Stott's work does do is undermine some of the assumptions about how previous vaccines have protected animals that have been challenged with injections of SIV. Animals will mount an immune response when presented with a foreign substance, called an antigen. "Everyone had assumed that [the immune response] had something to do with a response to SIV antigens," says Ronald C. Desrosiers of the New England Regional Primate Center in Southborough, Massachusetts. But Stott's experiments suggest that the protection is caused by some component of the T-cell line that the animals were vaccinated with—which would be unprecedented, says Desrosiers. "It's going to be scientifically interesting and important to sort out what's going on here."

But even Stott acknowledges that his work does not invalidate the hypothesis that HIV causes AIDS. Since the attenuated virus vaccine also afforded protection against subsequent challenge with SIV, "our findings do not, of course, exclude the possibility of a virus-specific component in protection," Stott writes. He adds that studies with viral antigens made from recombinant DNA technology—not grown in cell culture—may ultimately explain exactly how the vaccines are producing protection.

In the other study cited by Maddox as supporting Duesberg, physicist-turned-microbiologist Geoffrey W. Hoffmann and microbiologist Tracy A. Kion at the University of British Columbia showed that mice that had never been exposed to HIV could nevertheless produce antibodies to HIV antigens. In one case, animals from a strain that suffers from an autoimmune disease developed antibodies to HIV antigens spontaneously. In another, mice developed antibodies to HIV after they were exposed to cells from different mouse strains. Hoffmann's hypothesis is that certain HIV antigens resemble mirror images of normally occurring cell surface antigens that control response to foreign tissue. In some way, these mirror-image look-alikes trigger an autoimmune disease that produces the symptoms that resemble AIDS and even shares the same antibodies. But just because an AIDS-like disease *can* occur without HIV doesn't mean that it typically does, he asserts. "We have nothing in common with [Duesberg]'s idea that HIV has nothing to do with AIDS," says Hoffmann.

So how does Maddox explain why he leapt to that conclusion? "I'm not for a minute saying Duesberg is right in all points," says Maddox. "But I feel sorry that *Nature* has not done more to give his view prominence. It would have hastened the process by which the scientific community is coming around to the view that the pathogenesis of AIDS is more complicated than the baby-talk stories we were all given a few years ago." ■ JOSEPH PALCA