BOOKS: MEDICINE

Waiting for Vaccine

Robin A. Weiss

"Ever tried. Ever failed. No matter. Try again. Fail again. Fail better."

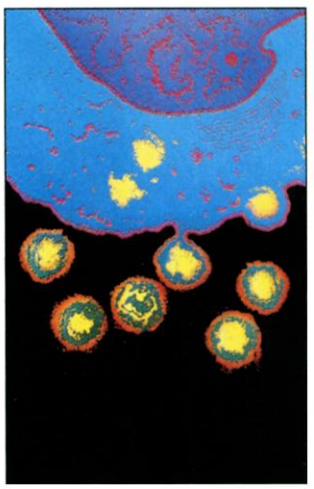
–Samuel Beckett

For many years Jon Cohen has provided readers of *Science* with excellent news coverage and incisive discussion of issues concerning HIV and AIDS. His articles are essential reading for the specialist and the observer alike. In this thought-provoking book, Cohen probes why we do not yet have a safe, efficacious vaccine with which to protect humans from HIV infection. With current estimates running at over 36 million HIV-infected men, women, and children (in addition to the 23 million who have already died as a result of AIDS since the disease was first recognized 20 years ago), Cohen addresses one of the most important goals of modern medicine and public health.

Cohen's readable book offers many perceptive vignettes on the "heavy-hitters" of research into HIV and AIDS. It takes us from the infamous 1984 press announcement of Margaret Heckler (the U.S. Secretary for Health and Human Services) that "We hope to have [an AIDS] vaccine ready for testing in approximately two years," through the subsequent highs and lows, complexities and false leads, to the situation today. We now have a number of reagents that elicit immune responses to HIV, but none have yet shown broad cross-protection to the virus that infects 15,000 people each day.

Shots in the Dark
The Wayward Search for an AIDS Vaccine
by Jon Cohen
Norton, New York, 2001. 458 pp. $27.95, C$39.99, £21.95. ISBN 0-393-05027-0.

Cohen's main thesis is that we could be much farther along the road to an efficacious vaccine if academic researchers, pharmaceutical companies, and funding agencies had pulled together under a single, coordinated leadership with a will to take selected vaccine candidates to extended experimental and clinical trials. As his paradigm, he cites the closely coordinated direction and momentum of the March of Dimes charity under Basil O'Connor's leadership, which supported the development of the Salk vaccine against poliomyelitis in the 1950s. Cohen calls for a "March of Dollars" to take forward the challenge of developing a vaccine for HIV. The March of Dimes cut through considerable academic prevarication to launch the trials, which effectively ended the polio epidemics that occurred each summer. Cohen does not, however, ask whether this decision to run exclusively with the inactivated Salk vaccine actually delayed the introduction of Sabin's live, attenuated vaccine, which eventually became the immunization of choice in the United States. Nor does he pause to consider why other successful vaccines, for example Max Theiler's yellow fever vaccine, did not require a March of Dimes.



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Cohen considers AIDS researchers as falling into two conflicting groups regarding a vaccine: purists, who wish to see the last detail of molecular biology bolted down before proceeding, and pragmatists, who would test imperfectly designed vaccines in order to learn from clinical experience and improve performance. Throughout the book, Cohen equates the purists with reductionists and pragmatists with empiricists, who would eschew theory for results. Yet in their pursuit of an experimental approach to scientific knowledge, the "reductionists" are the arch-practitioners of empiricism. Moreover, rational drug design, which was based on the reductionist molecular analysis of HIV replication, delivered pragmatic success: where available and affordable, combination antiretroviral therapy has reduced AIDS mortality by 60% or more. But Cohen makes his point cogently in quoting the veteran vaccinologist Maurice Hilleman: "The AIDS problem is so devastating that what you want is answers now and understanding later."

Cohen shows his surest touch on policy issues. His best chapters discuss the biotech companies, the liability issues of vaccines, and the arguments about universal and parochial ethics of vaccine trials. He might, however, have availed himself of more insight from scientists to consider why no vaccine against a lentivirus such as HIV has been successful thus far and to avoid such scientific half-truths as "Africa is home to most every infectious agent that has ever plagued humans." Home, yes; hearth, no.

I was fascinated to realize how differently a journalist and a scientist can perceive the same events. Cohen's unfolding story reminded me of Tom Stoppard's *Rosencrantz and Guildenstern are Dead*, in which the familiar scenes of Shakespeare's *Hamlet* are reset through the eyes of these bit-part players. Cohen's Hamlet of AIDS vaccines, a similarly flawed but visionary hero, is the late Jonas Salk. As a Guildenstern among the ranks of HIV-vaccine researchers, I saw Salk as the sideshow: a great figure from the past to be honored and humored at Cent Gardes Conferences, but one who crucially failed to grasp that HIV was not a rerun of polio.

Shots in the Dark is essentially focused on developments in the United States. Although Cohen meticulously discusses international conferences and trials in developing countries, his coverage of policy issues is centered entirely on America. He does not mention the fierce debates at the World Health Organization's Global Program on AIDS in the early 1990s or the reasons why this program was transformed into UNAIDS, which brought in funding from the World Bank and other agencies. He does not examine why UNAIDS still failed to provide a lead on the vaccine front nor the significant contributions to HIV vaccine research in Japan and the smaller European countries such as the Netherlands and Sweden. The author overlooks entirely the success and the reasons for the sad demise of Britain's AIDS Directed Program, which was set up exactly along the lines that he now advocates for efforts in the United States. Indeed, even when considering the U.S. Public Health Service, Cohen does not query why the Centers for Disease Control and Prevention has not been given more responsibility for AIDS vaccine programs than the National Institutes of Health. I would have preferred to see these issues discussed in place of the many pages Cohen devotes to the bickering among individual HIV researchers said by him to represent rival camps.

Shots in the Dark deals with vaccines largely in isolation from other public health measures for HIV in resource-poor countries. Yet the type of targeted, coordinated program that Cohen maps out should surely encompass additional approaches to AIDS prevention, because vaccines will inevitably have a long lead time. Over the next decade,

The author is at the Wohl Virion Centre, Department of Immunology and Molecular Pathology, University College London, 46 Cleveland Street, London W1T 4JF, UK. E-mail: r.weiss@ucl.ac.uk

condoms and vaginal virucides, could arguably have a far greater impact on curbing HIV transmission than candidate vaccines.

Nonetheless, I applaud Cohen's impassioned plea for a sustained, coherent HIV-vaccine program. On the book's dust jacket, Bill Gates and Seth Berkley, the president of the International AIDS Vaccine Initiative, do the same. Berkley's organization now has the budget to realize Cohen's vision. Let us hope that its leadership reads *Shots in the Dark* attentively. While Cohen decries the tortoise-pace of government bureaucracy and academic peer review, he also warns more subtly of the dangers of egotism and cronyism that can all too easily encroach on a wealthy nongovernmental organization.

BOOKS: COSMOCHEMISTRY

We Are Made of Starstuff

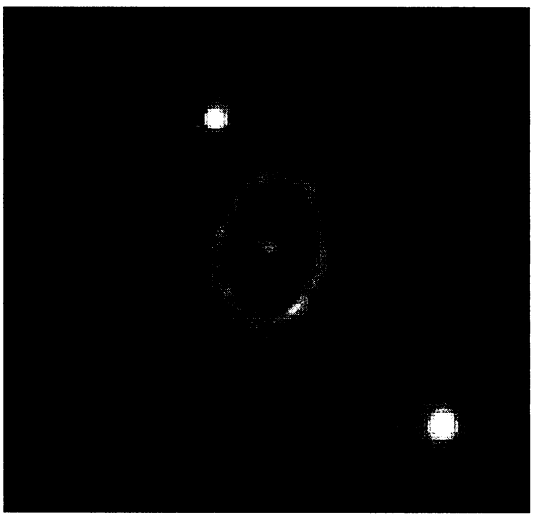
Craig J. Hogan

Marcus Chown's *The Magic Furnace* tells the story of how we came to understand first that the world is made of atoms and then how those atoms were made in the universe. It's an inspiring tale that bears retelling well, especially when famous anecdotes are freshened up with intriguing details. Did you know that Mendeleev was a bigamist and crossed swords with Tolstoy? and that he happened on the periodic table while he was using cards to organize information for a textbook? Or that Marie Curie's lab notebooks, still too radioactive to handle safely, are kept in lead-lined boxes? Emissions from her fingerprints still leave a record on photographic film inserted between the pages.

Chowan, a science writer and *New Scientist*'s cosmology consultant, revels in these sometimes heroic, sometimes melancholy or ironic, scenes from a romantic period of science: a handful of smart and curious people working on the ragged edge of academia, often in isolation or on borrowed time, who stumble around with good and bad hunches and make the best of their limited tools. The reader feels drawn into the way these scientists lived and worked, and into the way they thought about the problems they were solving. People whose names are known to scientists mainly for their important discoveries take on dimensions of real human beings. The orphaned and impoverished lens technician Josef von Fraunhofer is one example: After his fortunes were transformed by an industrial accident, he worked to calibrate the refraction of various glasses. In doing so, he eventually discovered the lines in the solar spectrum, which led to modern astrophysics.

Although Chown offers nonspecialists a fine modern account of the foundations of cosmochemistry, *The Magic Furnace* doesn't follow everything through to the state of the art. Readers won't find out that there are two fundamentally different types of supernovae, one powered like a thermonuclear bomb and leaving no remnant, the other powered by the gravitational energy of a forming neutron star. The author doesn't discuss how Standard Model physics now informs us about the interior structure of the quarks and gluons (which make up neutrons and protons) and about the formation by subtle neutrino effects of neutron-rich ("r-process") nuclei in supernovae. He doesn't mention that we now directly image giant sound waves oscillating in the primordial gas, waves whose properties confirm in detail many aspects of Big Bang cosmology; nor does he explain that we monitor oscillations of the solar plasma, which confirm knowledge of its deep interior. Perhaps there are now just too many threads to weave them all together into a really compelling story. Certainly, the picture is not as romantic as it used to be.

The Magic Furnace
The Search for the Origins of Atoms
by Marcus Chown
Oxford University Press, New York, 2001. 240 pp. $25. ISBN 0-19-514305-1.



Creative detonation. Rings of glowing gas encircle the site of supernova 1987A in the Large Magellanic Cloud. Supernovae produce heavy elements and scatter them into space.

Consider that irresistible, between-your-eyes starstuff idea: that your own "atoms of curiosity" come from the stars—a koan for the age of science that focuses thought on one's relationship with reality. I think even this sense of amazement has changed with the times.

One step in that change occurred when Fred Hoyle connected the idea of starstuff with what Chown calls "the most outrageous prediction in science." Hoyle calculated that stars can only make carbon, and hence humans could only exist, if the carbon nucleus has a resonance with a particular energy (7.65 MeV) that enhances the rate at which beryllium-8 nuclei capture helium nuclei at the prevailing temperatures inside stars. Willy Fowler subsequently confirmed that this resonance indeed exists; in Chown's words, "To this day, Hoyle is the only person to have made a successful prediction from an anthropic argument in advance of an experiment."

Although this remains a favorite story of we cosmologists, from a modern perspective the anthropic aspect of Hoyle's prediction seems less mysterious than it once did. Currently, we believe we know all the underlying equations that are important for the structure of nuclei, even if we can't compute everything that they predict and don't know what fixes the parameters or seemingly arbitrary coefficients that appear in them. It should not really be surprising that a resonance exists in carbon-12 somewhere close to the combined energy of beryllium-8 and helium-4; in the spirit of quantum mechanics, the carbon nucleus in this excited state can be regarded as a mixture of the two other nuclei. That is the mathematical nature of the resonance. The energy levels would agree approximately even if you fiddled with the parameters of the underlying forces that determine the structure of the nuclei, for about the same reason that some of the energy levels of atomic and molecular hydrogen approximately coincide. Also, getting the production rate of carbon right may not require very precise fine tuning of the resonance, because the structure of stars includes a built-in thermostat that automatically adjusts the temperature to just the value needed to make the reaction go at the correct rate. This is why stars remain stable for millions of years. Although Hoyle's insight was an intellectual triumph of theoretical astrophysics, it doesn't necessarily follow that the nature of physics is tuned by humanity's carbon production requirements.

It is, however, undeniable and astonishing that starting from a formless hot gas, atoms have developed a sense of their own history. Chown's book offers readers and their inner atoms an enjoyable introduction to that history.

The author is in the Astronomy Department, University of Washington, Box 351580, Seattle, WA 98195–1580, USA.