authors "prefer to think about the selection of heritable phenotypic traits, rather than genes." (p. 280) This is indeed a deeper, richer perspective for thinking about evolution, and is well-captured by the four dimensions of this enjoyable work.

MICHAEL LEVIN
Cytokine Biology Department, The Forsyth Institute, &
Department of Developmental Biology
The Harvard Medical School
Boston, Massachusetts
mlevin@forsyth.org

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Vaccine A: The Covert Government Experiment That's Killing Our Soldiers, and Why GI's Are Only the First Victims by Gary Matsumoto. Basic Books, 2004. 362 pp. $25.00 US, $34.95 Canada (hardcover). ISBN 0-465-04400-X.

After the first war in Iraq, in the early 1990s, returning veterans complained of a mysterious malady, whose symptoms included headache, memory loss, joint and muscle pain, fatigue, sleep disorders, and intestinal and respiratory ailments. Their illness often persisted and became debilitating. This sickness came to be called Gulf War Syndrome (GWS), although medical and military authorities never agreed that it is a single disease. Estimates of how many veterans suffered from GWS vary widely; the official Pentagon estimate is that about 1 percent of Gulf War veterans, or about 7,000 soldiers, have had illnesses with no other confirmed diagnosis.

What caused GWS was the subject of much speculation. Some suggested that affected soldiers might have been exposed—without anyone detecting it at the time—to nerve gas released when Iraqi weapons were destroyed, or that GWS was a reaction to the stress of battle. Neither theory is particularly consistent with available evidence, and the cause of GWS remains officially unknown.

In *Vaccine* A, investigative journalist Gary Matsumoto offers his own provoc-

ative explanation for Gulf War Syndrome. He asserts that GWS is an illness caused by adverse reactions to an anthrax vaccine that the Pentagon secretly administered to troops destined for the Persian Gulf war. He argues further that the military conducted an experiment on soldiers without their informed consent, that the Pentagon has covered up what happened, and that the truth needs to come out to avert repeat disasters. He asserts that several other vaccines that may soon come into use, including one for HIV and an anthrax vaccine now being stockpiled for use on millions of civilians in the event of biological warfare attack, contain the adjuvant squalene, which he believes is the agent that caused GWS.

This dramatic story line makes Vaccine **A** an intriguing read. Matsumoto is trying to alert his readers to an historical outrage with high stakes for the future, and his tone is prosecutorial; he has drawn up an indictment, not carried out a balanced investigation. A reader (or reviewer) may then act as a juror, weighing the evidence and trying to decide whether Matsumoto has proved his case.

My verdict: He has not. While Vaccine ***A*** offers strong circumstantial evidence to support some of Matsumoto's conclusions, in the end, his central thesis can be neither proved nor disproved, because of fundamental scientific uncertainties. Not to his credit, Matsumoto skates around some of the unanswered questions, and on at least two critical issues, fails to discuss pivotal existing evidence that tends to undercut his argument. But even with these weaknesses, the book raises some fascinating questions.

Here, in brief, is what Matsumoto believes happened: During the run-up to the first Gulf War, the Pentagon, alarmed by intelligence reports that Saddam Hussein had, and was prepared to use, anthrax biological warfare agents, resolved to immunize its troops against anthrax. The only licensed anthrax vaccine (then and now) was weak and, in animal tests, ineffective against several known strains of anthrax. Army scientists at Fort Detrick, MD, the national center for defensive germ warfare research, had tried to develop an improved anthrax vaccine for many years, by including so-called adjuvants, substances that boost the body's immune response, in the vaccine.

One adjuvant found effective in animal experiments was squalene, a naturally occurring lipid. Squalene is made in the human body, as a precursor to cholesterol, and occurs in foods and supplements such as olive oil and shark liver oil. When injected, as opposed to being ingested in foods, squalene stimulates the immune system and greatly enhances the effectiveness of vaccines. But animal studies also had shown that injected squalene has toxic side-effects. Not only does it amplify response to vaccines; it can also over-stimulate the immune system, leading it to mark squalene as a "foreign" substance and attack squalene in the body's own tissues. Animal experiments have linked injected squalene with auto-immune diseases, such as arthritis and lupus.

Matsumoto argues that as the first Gulf War loomed near, the Pentagon, with little time and few alternatives, accepted the risk of toxic side effects and vaccinated its troops with an improved, experimental anthrax vaccine ("Vaccine A") that contained a squalene adjuvant. He contends that GWS is auto-immune

disease, caused by squalene, in some of the vaccinated soldiers. He presents some two dozen case studies, veterans whose illness was diagnosed as an auto-immune disorder (or if not diagnosed, appeared almost exactly like diagnosed cases). Anecdotal case studies, of course, don't prove much, especially when they represent just dozens of the estimated thousands of GWS patients. But more compelling scientific evidence soon emerged to support the hypothesis.

Around 1995, two immunologists associated with Tulane University's medical school began testing GWS patients for anti-squalene antibodies. Immunological theory up to then had held that the immune system didn't react to lipids like squalene. If such antibodies were detected, it would establish two things: First, it would show that at least in some individuals, the immune system did react to squalene as is if it were an invading foreign substance. Second, anti-squalene antibodies are a distinctive "fingerprint" for prior exposure to squalene.

In a study published in 2000, the Tulane researchers reported that 95 percent (82 of 86) GWS patients they tested, all of whom had been vaccinated against anthrax by the military, had anti-squalene antibodies in their blood; in several control groups, including veterans not vaccinated for anthrax, members of the general public, and civilians with auto-immune diseases, none had anti-squalene antibodies (Asa et al., 2000).

Matsumoto, who was in touch with the Tulane researchers, wrote an article citing their data that appeared in Vanity *Fair* in 1999 (Matsumoto, 1999). In response to that article, the Pentagon denied that Vaccine A had ever contained squalene. Today, the military admits that it tested squalene-boosted anthrax vaccines in animal experiments—research Matsumoto documents in detail from public records and internal memoranda—but claims it decided not to use squalene in the vaccine administered to the troops during the Gulf War[1]. And, as Matsumoto concedes, he has no source—neither a whistle-blowing insider nor written records—proving that the military decided to use a squalene-boosted Vaccine A. This gap in his evidence chain seriously weakens Matsumoto's argument that GWS resulted from an experiment gone wrong, but it does not noticeably temper his accusatory zeal.

In response to the controversy provoked by Matsumoto's *Vanity Fair* article, the U.S. Food and Drug Administration (FDA), which licenses vaccines before they can be lawfully used and has not to date licensed any vaccines containing squalene, tested six lots of Vaccine A, and found squalene in five of the six lots. The levels were very low, parts per billion, but Matsumoto observes that the pattern of levels in different lots (each lot had roughly double the squalene content of the previous lot) looked very much like what would be used in a dose-ranging clinical trial. Subsequent tests of additional lots of Vaccine A confirmed similar low levels of squalene in about a dozen lots, all told. Why there was any squalene at all in the vaccine, when the Pentagon insists they had decided not to use squalene adjuvants, and why the squalene levels fit an apparent dose-ranging scheme, are very interesting but unanswered questions.

Following disclosure of the FDA test results, the Tulane researchers matched

specific lots of Vaccine A to patients with anti-squalene antibodies (Asa et al., 2002). In a few cases, serum samples were available from before and after vaccination, and showed antibodies to squalene after, but not before, vaccination. The total number of veterans for whom such data exist is small (around 100), and only the Tulane group has published on the subject, so far; confirmation by independent researchers would strengthen the case. Nevertheless, this is compelling evidence that at least some GWS patients were exposed to squalene in Vaccine A, and that their immune systems reacted. Whether this means squalene in the vaccine caused the illnesses suffered by these patients is not fully clear, but it's a strong sign pointing in that direction.

Does this mean that squalene in Vaccine A caused GWS? Matsumoto seems to think so, but his case is far from airtight. Several critical scientific unknowns remain:

First, while Matsumoto's case-studies of suffering veterans put a human face on an otherwise impersonal scientific investigation, the plural of anecdote is not data. We don't know how many of the 7,000 (or any other number one might accept) GWS cases fit the profile of the hundred or so that have been well studied. Without clinical details on a much larger number of afflicted veterans, we can't reasonably extrapolate from the few dozen well-documented cases to the larger group. Moreover, the Pentagon claims that 18 epidemiological studies have examined more than 500,000 veterans in total who received Vaccine A, and found no excess incidence of any disease linked to the vaccine[2]. Matsumoto doesn't even confront the existence of, let alone critically examine, negative epidemiological evidence from studies of Gulf War veterans. Instead, he seems more or less to assume that the handful of cases he describes represent all the veterans with GWS. This is a fundamental weakness in his argument, and leaves the reader with essentially no way to assess the size of the problem.

Second, if Matsumoto's hypothesis is true, it seems likely that some individuals' immune systems react to squalene and provoke auto-immune disease, while other people, although they may experience unpleasant side-effects immediately after vaccination, do not develop long-term, immune-mediated adverse reactions. What determines whether an individual is susceptible to severe, auto-immune side-effects? How many sensitive people are there in populations that might need to be vaccinated, and is there any way to identify them in advance? At this point, these are just important questions for research—the answers are unknown. Matsumoto recognizes this issue and treats it as an important uncertainty, but does not offer even tentative answers.

Third, and most critically, Matsumoto's analysis fails to deal adequately with the pivotal issue of low-dose effects. As mentioned above, while FDA tests (and other tests done since) have confirmed that several lots of Vaccine A contained squalene, the levels detected were in the parts per billion range; those concentrations translate into doses (the amounts of squalene in the injected 0.5 ml dose of vaccine) of about 5 to 40 nanograms (billionths of a gram) of squalene. Is it plausible that such tiny doses could stimulate the immune

response to the vaccine (the desired effect) and cause auto-immune adverse side effects? The FDA concluded that what it termed the "traces" of squalene it found were too low to be biologically meaningful. Matsumoto disagrees. In truth, the question is open scientifically, and there is some evidence to be weighed on both sides.

One might presume that a relatively large dose of squalene (or any adjuvant) is required to "turn on" the immune system--either beneficially, to induce immunization, or harmfully, to provoke an auto-immune response. As I noted earlier, squalene is present naturally at very low levels in the body; intuitively, then, it should take a relatively large dose to jump-start the immune system to attack, rather than ignore, this lipid. When it has been used as an immune-boosting adjuvant, it appears squalene is used in relatively large doses. Matsumoto cites a dose-ranging study by the manufacturer of a squalene adjuvant, MF59, which used doses in the range of 11 to 86 milligrams per vaccine dose—two million times greater than the doses in Vaccine A. This evidence strongly suggests, first, that nanograms of squalene in Vaccine A would not have boosted immune response, and second, if nanograms of squalene in Vaccine A can cause devastating illnesses, then milligrams in other vaccines must be enormously more hazardous. However, Matsumoto seems unwilling to confront these implications, and glides by the issue.

On the other hand, there are certain drugs, environmental pollutants, and natural substances like hormones and allergens that are known to cause effects at very low, even nanogram, doses. Allergic reactions, moreover, are mediated by the immune system, and after a patient has been "sensitized" by an initial exposure, very small doses indeed may provoke an adverse reaction. (Vaccine A was given as a series of shots, so a sensitization scenario is plausible.) Matsumoto interviewed a prominent immunologist who affirmed that, in general, substances can have biological effects at nanogram doses. But when he elicited that information, Matsumoto posed only the general question; he never asked his sources whether squalene, specifically, could plausibly have such low-dose effects. (He says he wanted to avoid getting biased answers, because opinions are so polarized over the safety of squalene.) Because of this evasive questioning, the key question—whether nanogram doses of *squalene*, which occurs naturally in the body at very low levels, can provoke auto-immune responses of the sort associated with some cases of GWS—was neither asked of nor answered by the experts Matsumoto consulted.

More seriously, Matsumoto also glosses over the most relevant evidence on the question that tends not to support his opinion. Numerous studies in various lab animals have shown that injected squalene provokes auto-immune disease. Matsumoto cites this evidence repeatedly throughout the book, and lists two dozen studies in a bibliography. He cites the animal data as evidence that the military ignored squalene's toxic effects, at soldiers' peril; he cites the same studies to support his inference that squalene in Vaccine A caused the illnesses of veterans with anti-squalene antibodies. Yet, curiously, when he discusses the fact that

Vaccine A contained only nanograms of squalene, he chooses not to examine the dosages used in animal studies. Obviously, knowing what doses produce such effects in animals can give us some insight on whether nanogram doses could have similar effects in GWS patients. The book's silence on this question is troubling.

As Matsumoto says, when castigating the Pentagon, the FDA and others for ignoring this evidence, the data are available on the internet via the National Library of Medicine's PubMed system; anyone can look them up. Using his bibliography, I spent an hour or so on PubMed, where I found the full text of half a dozen of his cited studies. The squalene doses that induced autoimmune diseases in animals, in those experiments, ranged from milligrams to grams—or roughly 10,000 to *one billion* times greater than the squalene doses administered to veterans in Vaccine A. Thus, while the effects seen in animals are *qualitatively* like the symptoms observed in some GWS veterans, the doses required to produce those effects in test animals were *four to nine orders of magnitude greater* than the doses veterans presumably were exposed to. This critical fact does not completely rule out a relationship between traces of squalene in Vaccine **A** and auto-immune disease, but it makes it seem less likely, or at least harder to explain.

Large doses are used in animal studies because experiments need to show effects in small groups of test subjects; linking effects with doses that produced harm in, say, one of 100 or one of 1,000 exposed animals would require impractically huge numbers of test animals. Since even effects that occur in less than 1 in 1,000 exposed individuals can be important public health concerns if the exposed population is large, toxicologists usually extrapolate risk estimates from large doses used in animal studies to the lower doses that people are exposed to. However, the margin between doses that are clearly harmful in animal tests and doses considered virtually certain to be safe for humans is ordinarily 100- to 1,000-fold or so. Few if any toxic substances are known to be harmful to people at doses a million- to a billion-fold below doses that harm test animals.

It is still theoretically possible that extraordinarily small doses of squalene might have caused auto-immune effects in some soldiers, especially if some individuals are far more vulnerable than average, for genetic or other reasons. Sensitization might occur, after which very small doses could elicit a response—in theory. But adverse responses to such ultra-low doses essentially fall outside the boundary of toxicological experience, and proving scientifically that the squalene doses in Vaccine **A** caused the observed illnesses would require crossing new scientific frontiers. Matsumoto is a journalist, not a scientist, and in *Vaccine A*, he is a prosecutor more than a journalist. The book nevertheless raises a provocative question for science to attack. Unfortunately for Matsumoto's prosecutorial argument, the answer is unknown and can't be known without extensive research.

While the unanswered scientific questions about GWS are central to whether the reader accepts Matsumoto's conclusions, the book also raises some broader issues, which Matsumoto does not effectively address.

The most important such issue is the policy ramifications of Matsumoto's belief that squalene caused auto-immune disease in some soldiers injected with Vaccine A. For policy purposes, we should ask "What if he's right?" and examine the implications for future military and public health policy decisions. Matsumoto claims that squalene is an adjuvant in several experimental vaccines that may soon be licensed to combat HIV, flu, herpes and other diseases. All vaccines have some adverse side effects; some individuals may even die after being vaccinated. Yet, society tolerates some acceptably low risk of side-effects, in order to have the benefits of immunity. The critical questions are, what is an acceptably low risk, and who decides?

Matsumoto refers in passing to such "risk/benefit" trade-offs, but does not explore the issue in any depth. For anthrax vaccine, the balancing act was actually a risk/risk/risk trade-off. First, there was the risk that Saddam Hussein might use anthrax weapons on alliance troops in Iraq. Assessments of that risk were based on intelligence that, we can see now, was not very accurate. Then, there was the risk of side-effects in the soldiers vaccinated against anthrax. Finally, there was the risk of *not* vaccinating the troops; if the Pentagon had decided that risk of the side-effects was too great and had not used Vaccine A, then Saddam *had* attacked with anthrax, the casualties—and the political recriminations—would likely have been severe.

The first and last of these are largely perceived risks—good data are difficult to come by, and uncertainties are vast. While some of the risks are to life and health, others are political hazards. Only on the second risk, the side-effects, can we get solid empirical data. But the data we have are not very good, partly because of intense controversy over GWS, and partly because of the secret nature of defensive biological warfare research. We need better risk assessments here, because the question will come up again. Indeed, troops sent to Iraq in the current war were immunized with Vaccine A. And if faced with a future large-scale biological warfare attack, we may have to decide whether millions of civilians should be given the same problematic vaccine.

The Institute of Medicine of the National Academy of Sciences has reviewed the available evidence, and concluded that Vaccine A appears to be "reasonably safe," while acknowledging major data gaps and research needs (Institute of Medicine, 2002). When society needs to weigh and balance such risks, decisions ideally should be reached democratically, in an open process, with evidence and different points of view effectively aired and difficult choices transparently debated. This is a decision most of us would prefer not to delegate to a few generals and White House staff, huddled in a Situation Room.

To support such decisions, we need much better answers than *Vaccine A* provides to critical questions: Did a few nanograms of squalene cause auto-immune disease in those GWS patients described by Matsumoto? How many veterans were given Vaccine A, and how many of those vaccinated experienced serious, lasting adverse effects? How badly do we need anthrax immunity? Is the known incidence of adverse effects an acceptable price to pay for it?

Unfortunately, we may never know the answers; the debate is so polarized that it may no longer be amenable to any consensus view of the evidence—which brings me to a second broader issue. The discipline of risk communication teaches that how one thinks and talks about a hazard largely determines how one's audience responds to that hazard. In recent decades, experts, journalists and others have learned, often from our mistakes, how to discuss risks (see Sandman, 1993). Without meaning to, *Vaccine A* describes a textbook case-study of how *not* to do risk communication.

Matsumoto's 1999 *Vanity Fair* article included several anonymous cases, soldiers who got sick after receiving Vaccine A. One of those cases, an airman at Dover AFB, identified himself on an internet site, and Dover was quickly abuzz, since he was far from the only one there who got sick after being vaccinated. Some airmen began refusing to be vaccinated–disobeying orders. The base commander suspended the vaccinations and demanded an investigation. With a mutiny brewing, the Pentagon sent a team of experts to Dover, where they held a press conference. Among the egregious risk communication errors made then and in subsequent statements were the following:

- The experts flatly denied any link between Vaccine **A** and the illnesses airmen had suffered, and attacked and tried to discredit evidence supporting a connection.
- To support their denial, they said, in effect, "Trust us—we're experts and officers."
  The experts either were largely ignorant of the facts (e.g., the Air Force's surgeon general), or were germ warfare researchers who had helped develop the vaccine and had obvious conflicts of interest.
- They made assertions that were easily shown not to be true—such as that there was never any squalene in Vaccine A, and that anti-squalene antibodies "occur naturally" in normal, healthy people.
- They attacked the victims, calling Dover airmen "malingerers, liars and whiners."
- They "shot the messenger" (Matsumoto), labeling him "reckless, irresponsible and wrong."
- They punished the commanding officer who had halted the vaccination program; he found his fast-track to General rank derailed, and soon left the military.

As any expert risk communicator would predict, this amateurish effort to quell a crisis had exactly the opposite of the intended effect: It greatly magnified outrage among soldiers and intensified distrust, giving affected soldiers and outside observers (such as Matsumoto) ample reason to believe that the Pentagon was lying to cover up a disaster. In short, the Pentagon's response polarized the debate. Matsumoto's rejoinder, *Vaccine A*, polarizes it further. Should the time come when we need a serious national debate on these very issues--for instance, if there is an anthrax attack larger than a few letters and the

government wants to vaccinate, let's say, the entire population of Los Angeles—we can only pray that decision-makers can fight their way through the impulse to cover up past errors on one hand, and the campaign to punish past sinners on the other, and make difficult decisions using the best available science.

Even if they do, the science is unlikely to be much better than what we have now. After several inconclusive Congressional investigations and expert committee reports, the consensus may be that GWS is both an "old" issue and one that's too hard to unravel, and limited research resources may flow to other priorities. It would be a shame if *Vaccine* A, with all its flaws, were the last word on the problem, but it may turn out to be just that.

I would be remiss if I failed to note a few stylistic shortcomings of the book as well. It is quite poorly organized. Important topics are taken up not once, but again and again, in succeeding chapters. Discussion of some critical topics is both fragmented—with key points scattered in different chapters—and numbingly repetitious, as Matsumoto makes the same points and cites the same evidence, again and again and again. *Vaccine* A needed, but clearly didn't get, a strong editing. It is also sprinkled with typographical errors and garbled sentences that stopped me in my tracks. These editorial problems are more than merely annoying; they suggest sloppiness, as if Matsumoto's zeal to make his case had vastly exceeded his good judgment.

Despite all its flaws, *Vaccine* A could, in the right circumstances, provide a list of questions that should be addressed before rolling out any major new anthrax vaccination program. That would be a public service, which Matsumoto clearly wants to perform. In my opinion, such a scenario is unlikely, but the book is there, if anyone is open-minded enough to use it. For that, and for his courage in pursuing this book despite withering attacks on his credibility, we owe Gary Matsumoto our gratitude.

EDWARD GROTH III
Groth Consulting Services
Pelham, New York
nedgroth@cs.com

Notes

[1] See http://deploymentlink.osd.mil/faq/faq_squalene.shtml. Accessed September 25, 2005.

[2] See http://www.anthrax.osd.mil/vaccine/safe4.asp. Accessed September 23, 2005.

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The Fallacy of Mother's Wisdom: A Critical Perspective on Health Psychology by Michael Myslobodsky. World Scientific, 2004. 451 pp. $38.00 (paper). ISBN 9-812-38458-8.

The 20th century saw significant changes in the practice of medicine. From an increasingly solid scientific base came striking discoveries, while, at the same time, patients became progressively more overtly demanding and distrustful of their doctors. Retreating from a besieged "paternalistic" identity, physicians, applying the "latest" findings of scientific and pharmacological research, adopted new roles as impersonal, sometimes distant, technicians and became enforcers of governments' health agendas.[1] Patients, feeling generally abandoned, often criticized, frequently confused and never satisfied, insisted on playing a greater role in their own health care.[2]

It was into the midst of these tectonic shifts that the sub-discipline of health psychology emerged. Back in the 1970s, in those early days when it first called itself "new," it exuded promise as it spawned a bio-psycho-social model, championed the fervour for "wellness," and rose rapidly to become a thriving aspect of the "psychology industry.'" Assuming the popularized public image of psychology as a science, it aligned itself both with medicine as a purveyor of medical knowledge and with patients (and potential patients) as a consultant and coach in healthy living. It was prepared to fill the interpersonal void in the doctor-patient relationship by offering a listening ear and caring presence as it empathized with the multi-layered aspects of sickness.

It is to this sector of psychology with its focus on physical health and "wellness" that Myslobodsky, in The Fallacy of Mother's Wisdom: *A* Critical Perspective on Health Psychology, addresses his attention. Spanning the breadth from psychological "cures" for cancer to psychological approaches to "the obesity epidemic" and the current quest for psychotropic prescription privileges, he looks critically at the role this sub-profession has been attempting to play in the health service arena.

Restricting himself to questioning the scientific basis of health psychology, the author examines its research foundation with only a few passing comments about the business edifice and its ability to "increase practice revenues" (p. 298) and "boost market share" (p. 298) that has been constructed upon it. (p. 9)