Biologist Stalks Malformed Frogs, Seeking Cause(s) of Their Distress

Alstead, New Hampshire

It's a horror story. And a mystery.

Biology graduate student Carol Drummond, who hopes to help solve it, has a few of the victims. Some are living in muddy glass aquariums in the back room of her farmhouse here. Others, who died, have been cleaned up, and placed in formaldehyde specimen bottles.

Drummond is the New Hampshire coordinator of the North American Amphibian Monitoring Program (NAAMP). It is a federal and states effort to identify the cause, or causes, of population declines and the epidemic of severely malformed frogs and salamanders that are now well-documented in the U.S. They also are known to be widely present elsewhere in the world.

Hers is a volunteer position: There's little money for scientists or for research on amphibian deaths and disability, she said here in an interview — although there is great public concern. When Drummond held a meeting for scientists and nature lovers worried about the frogs' decline, the state assigned her a room that holds 20 people. But 150 showed up to discuss the project's first goals: efforts to locate malformed frogs for study, and to gather baseline population data on New Hampshire's several species. They include northern leopard frog, green frog and bullfrog, as well as the mink frog, which Drummond says is North America's northernmost species.

Specimens Are Named

Drummond has been collecting the sad specimens that she and others find. “Semi-singleton,” for example is a male northern leopard frog with only one hind leg. He's resting quietly in an aquarium, eating the crickets she provides. Drummond had hoped to mate “Semi” with a similarly disabled female of his species, “Una.” But Una died recently, and has made the transition from swamp-water tank to formaldehyde bottle. So the mating — which might have helped shed light on whether the malformations are caused by genetic mutations — could not be done.

“Chester,” named for the character in Gunsmoke and “Pru,” as in pruned, are a pair of similarly crippled bullfrogs. Drummond hopes the will breed next year.

More horrendous to look at, but typical of deformities being discovered in New Hampshire and other U.S. locations, is a pickerel frog named “Poly,” who has an extra, fifth leg growing unnaturally on her back. Polymelia, meaning too many legs, is eerily similar in appearance to phocomelia, the seal-flipper malformation of the limbs that resulted, four decades ago, when pregnant mothers took the sleeping pill thalidomide. Some malformed frogs in fact have phocomelia, which means they possess hands or feet, but are missing the arms or legs.

Extra Limbs Are Peculiar

One tadpole, who is preserved, has two extra legs that emerge from the groin, between the two normal legs. These extra limbs, however, do not look like frogs legs: they are tentacle-like, without joints, and resemble octopus appendages.

The newest — and most upsetting — deformities, perhaps, which first were seen only this year in New Hampshire, are huge liquid-filled bubbles, some containing leg bones but little

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Doctors Finally Act to Control Alt/Med Methods

The medical profession is beginning to regulate physicians' use of alternative and complementary methods. The vehicle for these controls, according to the American Medical Association (AMA), is new regulations being written by the state medical boards that oversee doctors' practices (American Medical News Sept. 18).

The first state board to act, two years ago, was in Kentucky. A practitioner there, Kirk W. Morgan, M.D., had injected a patient with hydrogen peroxide to treat what he diagnosed as silicone leakage, Candida infection, and lupus erythematosus. Hydrogen peroxide injections are not established — or effective — therapy for any of these problems.

This case and several others prompted the Kentucky Medical Licensure Board to establish a policy on complementary care that includes guidelines on what not to do.

Bad Medicine Is Target

"We don't discipline doctors for using alternative medicine," explains board president Danny Clark, M.D. "We discipline them for practicing bad medicine."

Medical boards in Illinois, Alabama and Texas have established similar guidelines. In Tennessee, the state board has banned chelation therapy (except for heavy metal poisoning). Texas has written a special consent form for patients whose doctors plan to use alt/med methods.

Not all such efforts have succeeded. The North Carolina legislature, for example, killed a bill that would have made it a felony to offer the public injurious treatments. Supporters of the bill had cited the case of an 8-year-old diabetic girl who died after her naturopathic practitioner took her off insulin; he is awaiting trial for manslaughter (PROBE, Jan.).

Law Sought

The executive director of the North Carolina medical board urged the legislators to act, saying:

"We need a tough bill, because we are seeing health care revert back to where the public is in a 'buyer beware' situation. If a doctor is practicing forms of alternative medicine that are not harmful, then the board will not revoke or deny a license. But if competent evidence indicates the treatment has a safety risk, then we want additional criminal penalties for practitioners and the right to impose fines."

To move the regulatory program forward, the National Federation of State Medical Boards is preparing model guidelines for physicians who use alt/med treatments.

Better late than never! — D.R.Z.
Many Vaccines For AIDS Ready To Be Tested

Baltimore

The great gap in global AIDS control efforts now is the D in R&D: the development phase of the effort.

AIDS scientists meeting here last month at retrovirologist Robert Gallo, M.D.’s annual research conference were told by development facilitators that there now are a dozen candidate vaccines near ready or ready to be tested in human populations. By mixing and matching these immunologic preparations, more than 100 conceivable combination vaccines may be possible.

The problem, infectious disease epidemiologist Seth Berkley, M.D., of IAVI and microbiologist Peter Piot, M.D., of UNAIDS told the researchers, is the money, manpower, and, particularly, the political will needed to move these experimental preparations from the lab and into field tests of their safety and efficacy. (IAVI is the International AIDS Vaccine Initiative, headquartered in New York, which is bridging the gaps between science and the drug industry, between private funds and public finance, and between First World governments that can spend for health and Third World ones that can’t. UNAIDS, as its name indicates, is the United Nations’ lead agency in combating AIDS. The Baltimore conference is sponsored by the Institute of Human Virology [IHV], a part of the University of Maryland; Gallo is IHV’s founder and chief.)

In the scientific community, there is rock solid agreement that the only way to stop AIDS is to develop and deploy an effective vaccine. But, Berkley reported, vaccines still get only 2% of the global AIDS expenditures; they still count for less than 10% of research spending.

Advocates Were Absent

“Clearly,” Berkley said, looking back on the last two decades, “there were no advocates for vaccines.” There were of course many — vociferous — advocates for drugs that would save those already infected.

AIDS is now licking at Asia the way that it licked at Africa 15 years ago, before breaking out to overwhelm it. “Speed is the crucial issue,” Berkley declared.

The need is for $1 billion a year in international investment. Political willpower will be required to raise and effectively spend such sums, he added.

Leaders Take Note

Peter Piot, a Belgian who was the first to report widespread AIDS in Africa — in Zaire (now the Democratic Republic of the Congo) — said he was heartened earlier in September at the United Nations Millennium Summit conference of world leaders in New York: All of the African leaders save two — Kenya’s and South Africa’s presidents — cited AIDS in their speeches.

Ace Reporter Decries Death of Public Health

“The Collapse of Global Public Health.”

It is this subtitle for the book that grabbed our attention. The title is Betrayal of Trust (New York: Hyperion, 2000, $30), and the author is our intrepid and much honored colleague, Laurie Garrett, of Newsday, on Long Island. Garrett has covered Ebola, plague, AIDS and other killers up close, around the globe, becoming the dean of public health journalism.

Her phrase, “the collapse of global public health,” captures the conclusion to be drawn from hundreds of stories that she, we, and our colleagues have written over the last couple of decades: Illnesses, deaths, epidemics, even pandemics that could have been curbed or controlled — but weren’t. Diseases that doctors now know how to control, but can’t, because the methods offend people’s beliefs. Or, more importantly, because the resources — read money — and the necessary social organization and political resolve simply aren’t there. Not in filthy Indian cities where bubonic plague re-emerged a decade ago. Not in Africa, where medical care and public health are both essentially absent. Not even in wealthy America, where economic and racial disparities deny many their “inalienable rights.”

Social Needs Cited

Public health, Garrett writes, is or should be distinguishable from medical care. The one is a social benefit for everyone. The other is focused on the individual, meaning the person who can afford it.

Much of this book is Garrett’s retelling of her reportorial tours of hellholes abroad, and the greed, stupidity, and human disdain of the powers that be. Public health, unfortunately, is tied to politics. “An unstable, corrupt society is inevitably a public health catastrophe,” she says:

A sound public health system, it seems, is vital to societal stability and, conversely, may topple in the face of political or social instability or whim. Each affects the other: widespread political disorder or anti-governmentalism may weaken a public health system, and a crisis in the health of the citizenry can bring down a government.

So for much of the world, there may be no easy answers. There may be no answers at all. Can one imagine restoring public health in the Republic of the Congo, where President Laurent Kabila reportedly executed 8,000 of his citizens because they were witches?

How can public health officials operate under such conditions? Mostly, they can’t. So Garrett’s book is an encyclopedic account of the cruel, crass, and stupid ways governments frustrate doctors and
Tested... continued from previous page

as a priority. So, of course, did many leaders of developing nations. UN chief Koffi Annan, he added, identified AIDS as a “global issue.”

Until now, Piot said, “the world has looked the other way,” particularly with regard to Africa. Now, “AIDS is finally on the political agenda!”

Recounting his own travels in AIDS-stricken Africa, Piot noted that the disease ravishes human societies in the same way that it ravishes individual human bodies. There are 15 million AIDS orphans there. After the Black Plague in medieval Europe, Europeans needed a century to rebuild their decimated societies. The two plagues, he suggested, are comparable.

No one knows how long social repair from AIDS, once the epidemic is curbed, will require.

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Death... continued from previous page

other professional workers who know what to do, and are trying to help. Betrayal of Trust is a catalogue of deadly human folly.

Anger Is Manifest

Garrett, rightly, is angry, furiously angry. But her anger runs away from her; she can’t stop. The result: This is a blunderbuss of a book — 763 tight pages including thousands of references — that is filled with anger, rancor, and also, unfortunately, error. For example, thalidomide was not sold “to prevent miscarriages.” It was a sleeping pill. There is much, much too much here, some but not all of it well written.

Garrett’s global complaint about human folly and greed also leads her to embrace global remedies — and here her rhetoric conveys the neo-Marxian, New Left critique of capitalism, and societies like our own that are designed to serve individuals — well off individuals — at the expense of the masses. Even assuming that Garrett’s critique is correct, it is not at all clear to this reader and reviewer that corporate statism or the dictatorship of the proletariat would be any more responsive to human illness and need. The history of the last century suggests, in fact, that they would not.

Garrett, who is not a totalitarian, does understand this. She recognizes that effective public health infrastructures develop most readily in democratic societies. She deserves great credit for conceptualizing and characterizing “the collapse of global public health.”

Idealism Expressed

But in the very last paragraph of this vastly over-long volume, she slips back into the romanticism and idealism that motivate many of the very best disease fighters, as well as the reporters who cover their efforts.

“The new globalization,” Garrett writes, “pushed communities against one another, opening old wounds and historic hatreds, often with genocidal results. It would be up to public health to find ways to bridge the hatreds, bringing the world toward a sense of singular community in which the health of each one member rises or falls with the health of all others.”

We doubt this will happen. We don’t want to tie our health too closely with that of say, South Africans overwhelmed by AIDS. Most important, Garrett’s admonition, that it “would be up to public health to find ways to bridge the hatreds,” should, rather, have been the first sentence of her book, not the last. If there are ways that public health experts, or for that matter anyone else, can restore the right to life — and to health — to political agendas and governmental obligations, in autocracies as well as in democracies, those are things we badly need to know.

If Laurie Garrett has some ideas in this regard, we are eager to learn them!

— D.R.Z.
**Why Cig Story Ain’t Over Yet!**

A colleague has criticized our persistent tobacco coverage, saying, “David, your problem is that you just don’t like cigarette companies!”

Well, we don’t! And with cause!

First, the tobacco story is not over.

Second, there is much that can and should be learned from it.

At present, the story focuses on cig makers’ efforts to save and grow their enormously lucrative business at all costs, including the cost of millions of lives. Arrayed against them is the healthcare community, including particularly the World Health Organization (WHO), which this month plans to hold an international convention to curb tobacco products (PROBE, Sept.). We’re watching the news on this unprecedented event, which takes place mid-month, in Geneva.

**Company Papers Are Revealing**

What new lessons are we learning? Through the release of previously confidential company documents, we — all of us — are learning the illicit way these companies do business, and the factors that lead company decision-makers to do it. (Could you go to work each morning to make and sell a product that maims and kills its users?)

Is it denial, need, or greed that keeps people in the tobacco business? Or something(s) else?

Is this behavior unique to tobacco? Or is tobacco simply the extreme case of what any kind of company may do when it runs into trouble? Since the cigarette wars are now more than a half-century old, industry leaders and workers can be assumed, under the precepts of social darwinism, to represent extreme cases of denial, or whatever else may be involved — and hence are a fit subject for study.

Is it only Philip Morris? Or also Ford, Firestone, and Mitsubishi, and others, who will hide or deny risk to protect their companies and sales? Suppose it were your Ford Escort! Your spouse or kid!

Firestone knew about the problem five years ago; Ford, more recently. Neither told the government — or the public.

**Are Businesses Wolf Packs?**

Is company loyalty the highest value in 21st century business? It looks to us like it may be. This is called “pack loyalty” when it occurs in wild dogs or wolves.

This is why the cigarette companies, whose internal records have been forced out into public view by plaintiffs in lawsuits, remain critically important: They provide a window into corporate behavior. Ordinary corporate behavior, since only recently have Americans come to regard tobacco companies as corporate criminals — and begun treating them as such.

Look at it this way: Smoking has killed far more people than the Holocaust. It continues to kill far more people each year than the latter-day holocausts in Africa, Central Asia and the Balkans. (Ironically, as a perusal of the tobacco industry’s history shows, a significant number of major cigarette companies have been owned or operated by Jews.)

Our reading of the cigarette papers is that these companies are run, dictatorially, from the top. Loyalty to the company, the product, and the extraordinary profits are nearly absolute. Whistle-blowers are enemies.

**Is Johns Manville Any Better?**

That’s what the record shows about tobacco companies. But is it any different at Johns Manville, the asbestos biggy. Or at Dow-Corning, which made the breast implants and ignored the problems. Or at Bridgestone/Firestone?

We think the answer is that, by and large they — and perhaps this is human nature — all are the same.

We doubt that things are very different in other types of economics. Look at the Kursk! And Chernoby!

Our proposal is that the tobacco companies be thoroughly studied, as prototypes of industrial deceit and victimization of the public. Then, perhaps some economist or social theorist can come up with measures — a scale — of corporate anti-social behaviors. Various kinds of lies and sales methods, for example, could be characterized in this way. Then legal penalties could be rationally administered.

What could one call such ratings? To honor the folks who provoked its invention, why not call these torts tobacco factors! Is Firestone’s score one carton, or still just a few packs worth of irresponsibility? What about Ford’s? — D.R.Z.

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**Stalks... continued from page 1**

overlying flesh; they look like they were created by the Michelin tire ad artist. Drummond found these specimens only late in the summer, and neither she nor anyone else knows how and why they happened.

The census method being tried, is based on the annual North American Breeding Bird Survey. It calls for trained volunteers to travel designated rural routes at select times in the spring when the frogs are breeding — which means the males are croaking (the females are silent). The routes are set up so that the volunteers stop at a number of spots a half-mile apart, listen for and record the species and numbers of the frogs they hear in five minutes, then move on to the next station to repeat the process. The aim is to obtain baseline population data.

**Malformations Are Fatal**

The malformations, needless to say, are incompatible with life in the wild; most malformed frogs soon die and are eaten — or are eaten and die — unless they are discovered and captured. Timing is critical: The anomalies first appear when the animal metamorphizes from a tadpole to an adult frog, moves out of the water, and loses its tail.

*This coverage continues on following page →*
New Studies of Deformed Frogs

Populations of frogs, toads, and salamanders are facing two kinds of pressures. An expert says the two appear not to be related.

On the one hand, populations of some species seem to be declining — some have even vanished — particularly in the western U.S. On the other hand, different populations, particularly in the North and East, are experiencing frequent deformities like the ones Carol Drummond is finding in New Hampshire. But:

"There is no evidence that deformities have played a role in global amphibian declines anywhere," asserts Dennis B. Fenn, Ph.D., who is chief biologist for the U.S. Geological Survey (USGS), which has recently extended its purview from geology and geography to biological research; USGS is a part of the Department of the Interior.

In California, Fenn notes, where amphibian populations clearly are declining, federal researchers have examined some 8,000 frogs and toads from several thousand sites. Only 10 deformities were found. Many of the declines, Fenn adds, are occurring in environmentally pristine areas.

Most States Involved

Malformed frogs have thus far been found in 43 states. Some 38 species of frogs, and 19 species of toads, have been afflicted; malformation rates as high as 60% have been discovered in some local populations of these amphibians.

The USGS is the lead U.S. agency in efforts to sort matters out. A current part of this task is the recent publication of a report on the various types of deformities and the locations in which they were found, prepared by veterinary pathologist Carol U. Meteyer, D.V.M. She works at a recently opened USGS laboratory in Madison, Wisc. Meteyer closely examined more than 200 malformed frogs for the report.

"I think that the primary finding that came to light was that [different] sites have very different malformations," she said in a phone interview. "These malformations are probably happening very early, in the tadpole stage — and we are proposing that the causes of the various malformations are different."

Developmental Errors Suspected

In Vermont, for example, frogs collected for or by the USGS were missing part or all of their rear limbs. Some observers said that predators may have bitten off their legs. But Meteyer's x-rays show that many of these animals were missing parts of their hip bones, or even were missing the entire hip on one side, ruling out trauma as the cause. This "indicates a very early developmental problem," she explained, probably one that occurred before the tadpoles were a month old.

In Maine, by contrast, her observations and dissections uncovered few missing limbs or parts. But extra limbs and extra bones, including multiple hip bones, were common. Again, Meteyer says, this is a clear sign that the malformations were induced early in the tadpole's life, even though they may not have been manifest until later, during its metamorphosis from tadpole to frog.

In Meteyer's view, therefore, the problem is not a mutation or other type of error in the frogs' DNA. Rather, she thinks, the malformations are caused by an error in translating a frog's genome into developmentally appropriate limbs or other organs. Probably, she says, this is "an environmental factor." What is more, since these frogs do not survive to breed, this, too, rules against the malformations being caused by a mutation handed down from generation to generation. The research focus, she says in her report, published recently in the journal Teratology (vol. 62, pp. 151-71), is likely to be the tadpoles' limb buds.

Funding for this research is still low, but is rising. The USGS

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It's an extraordinary transition: The animal changes from a vegetarian, algae-eating swimmer, to a carnivorous, mosquito-and-bug-eating adult. (It thus serves two human needs, clearing ponds of scum when immature, and grabbing insect pests out of the air when mature, Drummond points out.)

Drummond presently is monitoring two farm ponds near her home here, both of which have yielded malformed frogs. We visited them together, wearing mud boots, to see if we could find any sick frogs, albeit the date, late in August, was a few weeks past the time that metamorphs usually appear.

One pool was the size of a baseball infield; the other added the one extra bone. Including multiple hip bones, were common. Meteyer closely examined more than 200 malformed frogs for the report. "I think that the primary finding that came to light was that [different] sites have very different malformations," she said in a phone interview. "These malformations are probably happening very early, in the tadpole stage — and we are proposing that the causes of the various malformations are different."

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Moreover, the pasture grass had been mowed to within a foot of the pond's edge. So there was no cover from predators, or from chemicals or light rays — ultraviolet light is one of the suspected causes of the malfunctions — to reduce exposure when the frogs are out of the water. The second pond was downhill from an apple orchard. Both ponds have rafts, rowboats or other human water play equipment. Clearly, a dizzying number of unnatural factors and combinations thereof affect these ponds — albeit frog loss and frog malformations have also been found in some of the most pristine areas of the country, say wildlife biologists who work for the Fed.

'Think Like a Frog!'

"To catch a frog, you have to think like a frog!" Drummond explained. Specifically, she added, frogs freeze when they sense s-l-o-w movement nearby. But they hop quickly away when approached by sudden movement that might be a hungry heron, a bass, or a biologist with a net.

So: Each of us was equipped with two nets, a large, long-han-
is the lead agency, and the program coordinator, Dan James, at its headquarters in Reston, Va., says they’ve had a $2.5 million increase in 2000. So USGS is now spending $3 million to $5 million a year on studying the status and trends of amphibian populations, he says. James is cautiously optimistic. “We’re beginning to know what all the pieces of the puzzle are,” he said by phone. “We just don’t yet know how they fit together!”

**Status Advance**

A few experiments have been conducted looking for the malformations’ causes. USGS biologist Donald Sparling, Ph.D., and his colleagues at the Patuxent Wildlife Research Center in Laurel, Md., sprayed a pool with a commercial preparation of the hormonal pesticide methoprene, which retards mosquitoes’ development. In 1997, they found a significantly higher malformation rate, of 15%, in frogs in this pool, compared to frogs in two untreated pools, where the malformation rate was 4% (which is still far above normal).

But when they repeated the experiment last summer (2000), it appears — from preliminary data — that methoprene was not associated with a higher rate of malformations than frogs in untreated control pools. Similarly, Sparling said, the Environmental Protection Agency (EPA) conducted a study last year in Minnesota, and found that methoprene did not boost the malformation rate. But UV light did.

Sparling’s conclusion as of now:

> “Probably multiple factors are involved.”

Meanwhile, a very ambitious set of experiments on causes of the malformations has been undertaken by a team of researchers anchored in the federal government, state wildlife departments in Minnesota and Vermont, and a commercial laboratory called the Stover Group, in Stillwater, Okla. They are comparing pond water and mud from heavily affected and less-affected ponds in the two states. One of the lead investigators is biochemist James G. Burkhart, Ph.D., at the National Institute of Environmental Health Sciences (NIEHS), located in Research Triangle Park, North Carolina.

**Teratogen Assay Is Used**

A major tool in these studies is a model assay system for developmental malformations, or teratogens, for which the experimental animal is a frog called *Xenopus* that comes from South Africa. Briefly, tadpoles of this species are exposed to suspected teratogens in their water for set periods, and then are killed, and examined for malformations. Pond water and mud were purified — thereby excluding bacteria and viruses as putative causes.

Both water and mud and the two together either killed or deformed significant percentages of the tadpoles, compared to water and mud from healthier, control ponds. The types and severity of the malformations produced in the lab reflected the morbidity and mortality occurring out-of-doors, in native frogs. “Strong correlations were observed among the results of . . . [the] in vitro bioassays, as well as between adverse and developmental effects in vitro and in the field,” the scientists reported last year (*Environmental Toxicology and Chemistry*, vol. 18, pp. 2305-15).

Going a key step further, the researchers subjected mud and water samples from the ponds to physical analysis using gas chromatography and mass spectroscopy. They detected several

Frogs Measured

In this way, she captured a dozen and a half small frogs in an hour at one of the ponds; this reporter failed to catch any. It clearly takes skill and speed, as well as knowledge, to do so.

This reporter was mostly stuck in the mud.

Returning to dry land, Drummond reached into the bucket and carefully extracted the frogs, one at a time. She gently turned them in her hands, so that each animal’s head extended out from between one thumb and forefinger. Then she measured its length, and examined it, paying particular attention to the hind legs.

The afternoon sun shone brightly, highlighting the small amphibians’ clear colors. “Their eyes are pure gold!” Drummond exclaimed. “Their bodies are green, and yellow, and tan — they’re beautiful!”

They were. And fortunately, all 18 frogs in this sampling appeared to be normal, as Drummond carefully turned them over in her hand, one at a time.

“I try to be very careful,” she explained. “Once, I broke one’s leg — and it cried out!”

“I . . .”

She paused.

“I wrote a poem about it!” she said.
Answers... continued from previous page

pesticides and industrial chemicals in the samples. When the Xenopus tadpole tests were repeated, using these compounds in the tadpoles’ water, malformations resulted that were similar to those found in the ponds where the samples originated. What is more, when the water and mud samples were purified and filtered using a very fine (0.2 microgram) filter or an elution tube, the samples’ toxicity diminished, as shown by Xenopus tests.

Thyroid Hormone Helps

The investigators found further — provocatively — that when they added thyroid hormone (thyroxine) to the samples, they “markedly reduced” the samples’ ability to cause malformed limbs in the tadpoles. Thyroid is an essential developmental hormone.

Different treatments of the teratogenic water and mud yielded different reductions in the various malformations, and some malformations occurred anyway. This leads Burkhart and his colleagues to say that “a complex mixture of both naturally occurring and man-made compounds was primarily responsible for the [teratogenic] effects observed in Xenopus [tadpoles].” Other factors, like UV light, may also play a role, they add.

Summarizing their findings thus far, Burkhart said by phone: “The studies we’ve done clearly indicate that there are factors in the water that contribute to malformations.” The group’s focus, he added, is not on single substances but on complex mixtures of chemicals and environmental factors — and on the possibility that these factors aren’t simply additive, but, rather, are acting synergistically in harming the frogs.

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