



### ANTIDEPRESSANTS AND CHILDREN

## Buried Data Can Be Hazardous To a Company's Health

A time-honored way to deal with negative results is to sweep them under the rug. Few ever get published. But New York State Attorney General Eliot Spitzer gave notice on 2 June that he may punish companies suspected of burying clinical data. This drew cheers from researchers who have been campaigning for a public registry of all clinical trial results—whether positive or negative—as well as those opposed to the use of antidepressants in children.

Spitzer filed suit in a New York court charging the U.K.-based drug firm GlaxoSmithKline (GSK) with “repeated and persistent fraud,” alleging that it had promoted positive findings but hadn’t publicized unfavorable data on children and adolescents who were treated for depression with its drug paroxetine, also known as Paxil. The company engaged in “illegal and deceptive” reporting, according to Spitzer, by minimizing reports of suicidal thinking among patients and misleading doctors into overprescribing the drug. The suit asks GSK to “disgorge” millions of dollars.

GSK responded with a one-page note saying that it had “acted responsibly” and that “all pediatric studies have been made available ... to regulatory agencies worldwide.” The company also circulated a detailed letter it sent out this spring updating physicians on potential suicide risks, a follow-up to a public review organized by the U.S. Food and Drug Administration (FDA) (*Science*, 6 February, p. 745). GSK’s letter says that “it is not yet clear whether antidepressants contribute to the emergence

of suicidal thinking and behavior.”

Spitzer’s allegations fell like a live grenade among other drug companies, but they had little to say. Industry spokesperson Jeffrey Trehwitt of the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, D.C., declined to discuss the potential impact on clinical reporting. But PhRMA is on record, Trehwitt said, in support of the proposal to report all clinical trial results.

The suit has energized the campaign to create a clinical trial registry. “I’m just thrilled with Spitzer,” said one champion of this effort, Drummond Rennie, an editor at *The Journal of the American Medical Association*. Members of the American Medical Association (AMA) will consider a proposal endorsing a

**Rattling cages.** Spitzer has accused GlaxoSmithKline of “persistent fraud” in selling antidepressants.



### GSK's Reanalysis of Risks

GSK study	Final report	Suicidal ideation* on Paxil	Suicidal ideation* on placebo
329, M. Keller <i>et al.</i>	2001	5.8%	1.8%
377	1998–99	4.8%	10.6%
701	2000	18.8%	16.0%

\* Emergent suicidal ideation includes self-injurious remarks or behaviors related to suicidal ideation, suicide attempts, self-inflicted harm, or overdoses.

national clinical trials register at their annual meeting 14 to 16 June in Chicago.\*

Spitzer’s suit also drew praise from critics of psychoactive drug use in children. “I hope this will clean up the mess in psychiatric drugs,” says Vera Sharav of the Alliance for Human Research Protection in New York City.

But some psychiatrists who have prescribed antidepressant drugs in the category that includes paroxetine—the selective sero-

\* AMA Council of Scientific Affairs Report 10-A-04.

tonin reuptake inhibitors (SSRIs)—fear that this punitive action will muddy the waters. Harold Koplewicz, director of New York University’s Child Study Center, says, “I have great respect for Eliot Spitzer ... but I’m concerned about this lawsuit” because it will further discourage use of SSRIs to treat depression in children. He’s not persuaded that paroxetine is significantly riskier than other SSRIs, such as fluoxetine (Prozac), which is widely viewed as safe. The big issue, as Koplewicz sees it, is that all SSRIs must be carefully monitored in the first weeks of use in all ages because they have a “disinhibitory” effect.

Spitzer’s lawsuit focuses mainly on three trials of paroxetine to treat major depression in children and adolescents, all funded by GSK (see table). Only one was published: study 329, led by psychiatrist Martin Keller of Brown University. Keller could not be reached for comment, but Koplewicz, who participated in the trial, said Keller organized it and solicited funding from GSK because he wanted to fill a gap in information on how children respond to this type of drug therapy. Keller’s group reported in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2001 that, based on a randomized, placebo-controlled trial in 275 people, “paroxetine is generally well tolerated and effective for major depression in adolescents.” GSK circulated these words far and wide.

Spitzer’s complaint, however, charges that none of the studies produced significant evidence that paroxetine is “efficacious” in treating depression in this age group and that the two unpublished studies “failed to show that paroxetine was more effective than placebo.”

Keller’s study identified one serious adverse event (headache) that might have been caused by the drug. But Spitzer’s complaint alleges that there were more significant problems. Citing study data, it states that 6.5% of patients on paroxetine showed “emotional lability”—the term that covers suicidal thinking—versus 1.4% for those on placebo. The percentages were also higher for patients on paroxetine in the two unpublished studies, Spitzer charges. And his complaint says that, “combined, studies 329, 377, and 701 showed that certain possibly suicide-related behaviors were ap-

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Symbols of  
ocean pollution

1587

The sun's  
nearest  
neighbors

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Genome  
comparisons  
spring surprises

proximately two times more likely in the paroxetine group than the placebo group.”

Spitzer's complaint alleges that GSK “repeatedly misrepresented the safety and efficacy outcomes” from these studies in internal memos to its sales force and in medical letters to physicians mailed between November 2001 and January 2003. In addition to holding back negative findings, GSK failed to point out that hints of efficacy in study 329

lacked statistical significance, Spitzer claims.

The apparent conflicts in GSK's data records came to light as GSK applied to drug authorities to win approval for pediatric use of paroxetine. As British, then Canadian, experts pored over the data, they challenged GSK's claims in 2003. The U.S. FDA held a review earlier this year and on 22 March issued a “talk paper” asking SSRI manufacturers to include new warnings that patients on

SSRIs should be closely monitored.

In its 2004 medical letter, GSK clarifies two points: Combined data on paroxetine “did not show a benefit for the treatment [of depression] in pediatric patients,” and “the incidence of adverse events possibly related to suicidal behavior” in pooled data on 1100 patients was 2.4% for those on paroxetine versus 1.2% on placebo. But, GSK adds, “no patients committed suicide.” —ELIOT MARSHALL

## IMMUNOLOGY

## Unexpectedly, Ancient Molecule Tied to Asthma

A surprise discovery in mice has linked a mysterious, largely unexplored class of molecules to asthma and may bolster the theory that the respiratory disease is a misplaced reaction to parasites. The molecules, called chitinases, were long considered a primordial response to certain parasites and insects; chitinase breaks down the compound chitin, which is produced in the shells and outer surfaces of these animals.

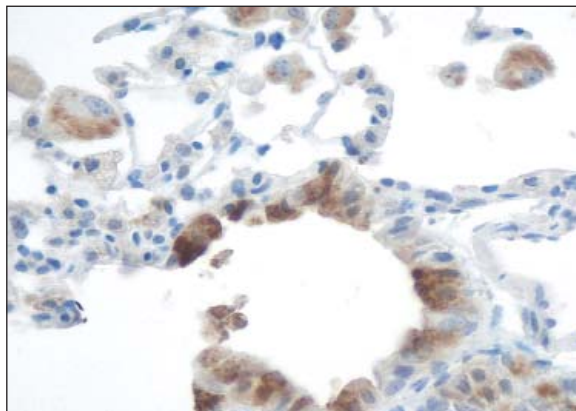
Because humans don't produce chitin, their half-dozen or so chitinase genes have often been dismissed as relics of evolution, although one has been linked to an inherited disease. Now, on page 1678, Yale University School of Medicine pulmonary specialist Jack Elias and his colleagues have tied a second chitinase, an enzyme called acidic mammalian chitinase, to a classic inflammatory response in asthma.

“I think it's going to open up a whole new area of exploration,” says William Busse, an asthma specialist at the University of Wisconsin Medical School in Madison. “A lot of people would have given up and said, ‘This [chitinase] has nothing to do with anything.’ They pursued it.”

The pursuit, however, came 2 years after the scientists mistook early evidence for something more mundane. Elias, pulmonary scientist Zhou Zhu, and others had noticed crystals in the lungs of mice bred to have an asthmalike disease. They assumed that the crystals were the same as those commonly seen in the sputum of asthma patients. Finally, “someone in my lab said, ‘Let's make sure,’” says Elias. After purifying the crystals, the researchers were astonished to learn that they'd hit on a chitinase.

Intrigued, they began tracing the chitinase path in asthma. First, they induced asthma attacks in their mice and then examined

their lung tissue. The scientists found far more of the chitinase there than in the lungs of healthy animals. Then they focused on a class of T cells, T helper type 2 (Th2) cells, that many consider critical to triggering asthma. Th2 cells, Elias's team found, prompted levels of the chitinase enzyme to soar. Interestingly, overproduction of the chitinase seemed to depend on a key Th2



**Spotting chitinase.** In mice with an asthmalike disease, chitinase (dark brown) shows up in lung tissue.

cell protein, interleukin-13 (IL-13). Extra IL-13, common in the lungs of asthmatics, is thought to help spark asthma attacks.

When Elias and his colleagues gave the sick mice a serum that blocked the chitinase, the animals' lung inflammation eased. The drug, however, didn't alter levels of IL-13 and other Th2 cell proteins. This suggests that the chitinase is a domino that falls later than IL-13 and other Th2 molecules when they precipitate asthma. It also suggests, says Elias, that the chitinase may be a new drug target for asthma; Yale has licensed patents on the discovery to MedImmune, a biotechnolo-

gy company in Gaithersburg, Maryland.

The scientists also studied lung tissue from humans with asthma and from healthy controls. Those with asthma had high levels of the chitinase in their lungs; the chitinase was undetectable in those without the disease.

That pattern reminds Rolf Boot, a biochemist at the University of Amsterdam, the Netherlands, of what he's seen of another chitinase in Gaucher disease, a rare enzyme disorder. Boot and his colleagues, who were also discoverers of the acidic mammalian chitinase that surfaced several years later in Elias's lab, have found that in Gaucher patients, a second human chitinase can reach levels 10,000 times higher than normal. Like acidic mammalian chitinase, the function of this other chitinase is a mystery.

Although the Elias work sheds light on acidic mammalian chitinase, it also “raises a lot of questions,” says Marsha Wills-Karp, who directs immunobiology at Cincinnati Children's Hospital Medical Center in Ohio. It's still uncertain whether the discovery that asthmatics overproduce a chitinase bolsters the popular theory that in asthma patients, the body senses parasites where there aren't any and sends the immune system into overdrive. But if that's the case, says Wills-Karp, chitinase should be among the first dominoes to fall in reaction to something in the environment, followed by overproduction of various Th2 molecules and then an asthma attack. “There may be more to the story, something we're missing,” she says, and she hopes that further study of the chitinase will fill in any gaps. —JENNIFER COUZIN