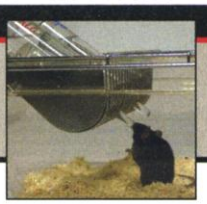

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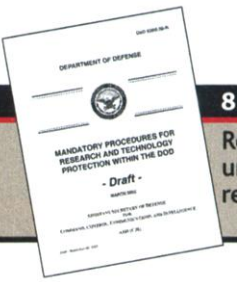
New model for alcoholism



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Restricting unclassified research

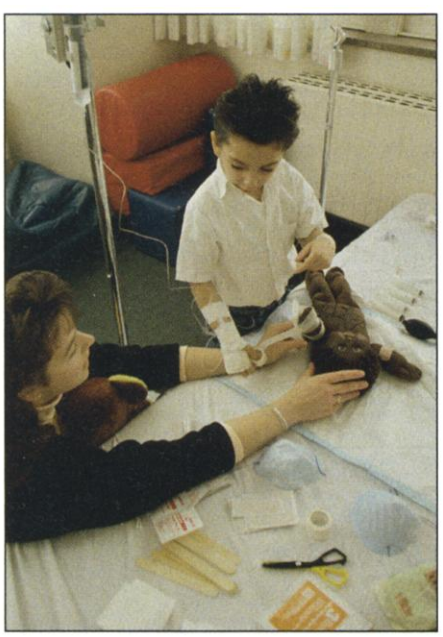
PEDIATRIC DRUG TRIALS

Challenge to FDA's Authority May End Up Giving It More

In a recent 4-week period, the U.S. government reversed course twice on whether drugmakers should be compelled to test their products on children. The policy went from "yes" to "no" and then back to "yes"—confusing researchers and companies alike. The muddle ended 19 April, when the Bush Administration came out in favor of retaining a 3-year-old rule that gives the Food and Drug Administration (FDA) power to demand that companies conduct targeted studies to learn about side effects and set proper doses for children.

Clinicians and child-health advocates—who lobbied for this outcome—are upset about the flip-flop and want to ensure that it won't happen again. Several senators responded this week by proposing to give FDA permanent authority to order such clinical trials.

The furor was sparked by a lawsuit filed in 2000 seeking to curtail FDA's power. The Competitive Enterprise Institute of Washington, D.C., and two other free-market advocacy groups challenged FDA's authority to carry out what the agency calls its "pediatric rule." In force since 1999 but used sparingly, this rule enables FDA to ask for pediatric tests of any drug being developed for adults that might also be given to children. The aim is to look for unexpected effects and set proper doses.



Filling a need. After the Administration flip-flopped on whether FDA should have power to require pediatric drug trials, Congress is stepping in.

But the three groups viewed the pediatric rule as an economic burden and a restriction on the practice of medicine, claiming that the effect would be to "delay new drug approvals and to enlarge FDA's power beyond the limits set by Congress." They sued to stop it. (FDA's new chief counsel, Daniel Troy, helped draft the suit when he was in the private sector, but he has recused himself from the matter at FDA.) In March, FDA informed the court that it would not fight the lawsuit; the agency said it would suspend the pediatric rule while it studies its impact. This prompted an uproar.

FDA took "a massive step backwards," says Mark Isaac of the Elizabeth Glaser Pediatric AIDS Foundation. "We were appalled" by FDA's failure to defend its authority. That feeling was widely shared. FDA's decision "surprised and dismayed" members of the American Academy of Pediatrics (AAP), says Richard Gorman of Ellicott City, Maryland, who chairs AAP's committee on drugs.

At the heart of the dispute is whether incentives are enough to get companies to study pediatric effects, or whether mandatory authority is needed. FDA has had a program since 1997 that offers big rewards for doing pediatric trials. Companies can get a 6-month extension of an exclusive patent on a drug if they do research that defines doses for children. More than 50 drugs have been reexamined and 29 relabeled in this way. In one case, FDA learned that children receiving a pain and seizure medicine were being underdosed by 30%; another trial found that young children given an anaesthetic had a higher than expected risk of seizures. The incentive program is so popular that Congress enacted a law last year extending it through 2007.

But AAP and the child health groups argue that the pediatric rule is needed to fill gaps in the incentives program and overcome companies' unwillingness to include children in clinical trials of some drugs. Philip Pizzo, dean of medicine at Stanford University and an expert in pediatric AIDS and oncology, says that industry had "not made the co-development of drugs for children a priority" until FDA began nudging it. He thinks the pediatric rule is "enormously important."

And as Gorman points out, the incentives program covers only drugs. It leaves out vaccines and other nonpill biopharmaceuticals, a category that includes some of the most promising new therapies being produced by molecular biology. In addition, incentives may not work if a drug's use is being expanded to cover a new disease, Isaac says, because the company gets the patent bonus only once.

Furthermore, several pediatric oncologists meeting at an advisory panel of the Institute of Medicine in Washington, D.C., last week said that companies usually refuse to allow new, experimental cancer drugs to be given to children. They consider it too risky. That leaves doctors with few options, said a frustrated Peter Adamson of the Children's Hospital of Philadelphia: "We continue shuffling existing therapies ... like deck chairs on the *Titanic*." AAP's Gorman adds: "The exciting thing about the pediatric rule is that for the first time, it puts children's needs at the table" when new drugs are being considered at FDA. He thinks this could radically change the way companies plan and develop new drugs.

AAP, the Pediatric AIDS Foundation, and a dozen other organizations lobbied Congress and the president seeking to put FDA back on its original track. As criticism mounted, Secretary of Health and Human Services Tommy Thompson intervened. On 19 April he issued a statement saying, "We will enforce and improve the FDA's pediatric rule." He also promised to increase the amount of aid to high-priority pediatric trials from $4 million to $7 million a year. The money will go to a network of academic labs supported by the National Institute of Child Health and Human Development.

But the turnabout did not halt a political reaction. Two Democratic senators—Hillary Clinton (NY) and Christopher Dodd (CT)—joined Republican Mike DeWine (OH) to

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propose that FDA get full legal power to order pediatric trials, and on 29 April they introduced a bill to that effect. The attempt to curb FDA's authority may therefore have done just the opposite. **–ELIOT MARSHALL**

PALEOBOTANY

Fossil Plant Hints How First Flowers Bloomed

Some 65 million years ago, a riot of flowering plants burst upon the world. Where did they come from? That question, which Charles Darwin called an "abominable mystery," has perplexed evolutionary biologists ever since. Now a remarkably well-preserved fossil from China promises to unveil the murky ancestry of this most diverse group of plants, in a surprising way. "This may be the most significant fossil flowering plant ever found," says Peter Raven, director of the Missouri Botanical Garden in St. Louis.

Like a rose. The 25-cm-high *Archaefructus* resembled modern flowering plants.

The 125-million-year-old plant—which a team of paleontologists led by Ge Sun of Jilin University in Changchun, China, and David Dilcher of the Florida Museum of Natural History describes on page 899—suggests that the forebears of flowering plants may have been aquatic, weedy herbs. Most paleobotanists have long believed that flowering plants, or angiosperms, arose instead from woody plants resembling the magnolia tree. That made sense, because the closest known relatives of angiosperms—the conifers and other so-called gymnosperms—are all woody. Indeed, the latest genetic studies suggest that the most primitive living angiosperm is *Amborella*, a woody shrub in New Caledonia.

Enter *Archaefructus sinensis*, fresh from the lake deposits of Liaoning Province in northeastern China. A closely related species from Liaoning came to light in 1998 (*Science*, 27 November 1998, p. 1692), but like most plant fossils, it was fragmentary. Then, in summer 2000, Qiang Ji, now at the Geological Institute of the Chinese Academy of Geosciences, showed Dilcher a slab of rock from Liaoning that contained a much better specimen, one that preserved intact the entire plant from roots to flowers. "I had to sit down, I was so impressed," Dilcher recalls.

The plant has clear flowerlike traits. The female reproductive structure, called the carpel, is closed with seeds inside. The male organs, known as anthers, resemble modern ones and lie below the female parts, a classic hallmark of flowers. But *Archaefructus* would raise a florist's eyebrows: It has no sepals or petals, and most strangely of all, its stamens come in pairs rather than singly.

To find out where *Archaefructus* fits within the botanical family tree, coauthor Kevin Nixon of Cornell University plugged 16 such traits into a computer programmed to calculate likely evolutionary relationships. The program compared the features with those of 173 living plants, whose own relationships were strengthened by 1600 molecular markers. *Archaefructus* came out as the sister group to all living angiosperms, even closer to the common ancestor than the woody *Amborella*.

If the team's analysis holds up, *Archaefructus* could have a lot to say about the earliest angiosperms. Its characteristics support the idea that early angiosperms were herbs. Herbs grow faster and reproduce younger than other seed plants do, and that could have given them an edge over slower growing competitors. Because every branch tip on *Archaefructus* ends in a flower, paleobotanist Bruce Tiffney of the University of California, Santa Barbara, infers that *Archaefructus* had a short, fast-growing life. "This is the best evidence so far" for herbaceous early angiosperms, he says.

It may also have lived in water, Dilcher says. The presence of fish fossils in the same type of rock, the plant's delicate stems, and its bulbous structures that may have served as floats all hint that *Archaefructus* grew in lakes. Early herbs may have thrived in watery habitats, Dilcher speculates. There, free of competition from other seed plants, early flowering plants could have bloomed into new shapes.

Dilcher and his colleagues also think that *Archaefructus* helps explain some of the steps in flower evolution. The paired stamens, Dilcher says, are consistent with the idea that angiosperms once bore their male and female reproductive organs on separate shoots. As these shoots evolved to be shorter, the sexual parts came into the close proximity now seen in modern flowers. "It's very tantalizing," says Dennis Stevenson of the New York Botanical Garden.

But although many other experts are equally smitten by *Archaefructus*, they say they won't be swept off their feet until they've had a closer look at the characters used to establish its evolutionary position. "A whole lot depends on whether [*Archaefructus*] is correctly positioned in the tree," says Michael Donoghue of Yale University. If it is, then they may begin tossing roses.

–ERIK STOKSTAD

WEAPONS LABS

DOE Delays Hiring of Livermore Head

The scheduled appointment of a new director for Lawrence Livermore National Laboratory in California was delayed last week in the latest sign of tension between the lab and its two overseers, the University of California (UC) and the Department of Energy (DOE).

DOE officials say they just wanted more information on the slate of candidates drawn up by UC, which runs the labs for DOE, that was to be presented 26 April for action by the Board of Regents. The leading candidate is believed to be physicist Raymond Juzaitis, currently a senior administrator at Los Alamos National Laboratory. Sources say that the long-running rivalry between the two weapons labs may have played a role, along with the fact that Juzaitis once supervised Wen Ho Lee, the former computer scientist at Los Alamos who was caught up in allegations of spying but never charged with espionage.

CREDITS: G. SUN *ET AL.*