La Jolla Biologists Troubled by the Midas Factor

Under the pressures of commercialization, a question of scientific etiquette among molecular biologists has mushroomed into a dispute involving a multimillion-dollar patent claim

La Jolla, California. Researchers from three leading academic institutions which are all close neighbors in this opulent cliffside suburb just north of San Diego have become embroiled in a vexed priority dispute over a research method that is also a potentially lucrative new way of producing synthetic vaccines.

Articles describing the essence of the new method were published almost simultaneously last fall by two teams of researchers, one from the Scripps Clinic and Research Foundation, the other from the La Jolla–based campus of the University of California, San Diego (UCSD), and the Salk Institute.

The UCSD/Salk team was first in submitting their manuscript for publication, by a margin of 5 days, but the Scripps group was first to file a patent application and to exploit the commercial value of the idea. Synthetic vaccines "would be the biggest thing Scripps ever ran into in terms of additional revenues," Scripps president Charles C. Edwards told the San Diego *Union*.

The institution has already parlayed its patent claim for the method into a rich commercial connection, a joint venture to produce the synthetic vaccines with the medical supply company Johnson & Johnson. The company will pay Scripps an undisclosed sum, said to be $30 million, which will include funds for a new research building.

At the root of the intricate edifice of disagreement is one agreed fact. At a meeting in March 1980, Russell Doolittle of UCSD told Richard Lerner of Scripps about his colleague's use of the new method, and the Scripps team passed over the occasion to mention, as they now state to be the case, that just 2 or 3 days earlier they had ordered materials to put the same new method into practice. From that moment of silence has grown a complex dispute, prompted by the commercial value of the idea, about scientific etiquette and the exact nature of what, if anything, the Scripps group learned from the rival team.

The commercialization of molecular biology is sometimes said to be more problematic than is the case with other sciences because its basic and applied aspects lie so close together. Vannevar Bush's quip that the difference between basic and applied science is "about 20 years" may still often be true in chemistry or engineering. With molecular biology, the gap seems sometimes to have shrunk to a matter of weeks. In the case of synthetic vaccines, both the Scripps and the UCSD/Salk teams say they conceived of the commercial use of the technique before even publishing their respective descriptions of its use as a research tool.

Both teams say they wrote down descriptions of how to make vaccines by the new method, and it is these descriptions that will presumably determine the priority of inventorship for patent purposes. Patent applications remain confidential until a patent is issued, and the exact nature of each team's position remains a matter largely of conjecture. The University of California declines to say even whether it has yet filed a patent application. What has come into controversy is not the respective patent positions but an issue that could be closely related, the development of the synthetic vaccine method as a research tool.

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As a research tool, the method is in essence a way of identifying proteins immunologically by chemically synthesizing their antigenic sites: the synthetic antigen can then be used to stimulate antibodies against the protein or virus from which it comes.

Now that the nucleic acid sequence of many viruses is being determined by the new rapid sequencing methods, the amino acid composition of their proteins can be inferred via the genetic code. Computer programs also enable one to predict how the protein chain will fold itself up, and in particular which regions of the chain are likely to lie on the outside of the mature molecule. It is in the outside regions of the chain that the sites recognized by the immune system are located. These sites also happen to be sometimes quite small, defined in some instances by no more than a ten-amino-acid section of the protein chain.

A peptide of ten or so amino acids can readily be synthesized from chemicals off the shelf. Injected into the body in appropriate form, it will raise the same or similar antibodies as would be produced against the full virus protein. For the researcher, these antibodies are powerful tools for identifying viral proteins. In the medical context, it is the raising of such antibodies that is the purpose of vaccines. Synthetic antigens, if they work, would be purer, safer, and maybe cheaper than conventional vaccines, which consist of the killed or attenuated whole virus and sometimes debris from the culture medium as well.

Most elements of the idea seem obvious enough, so much so that some researchers express surprise at the idea of its being novel enough to be patentable. But in fact no one seems yet to have put all the elements together in a published recipe for going from virus nucleic acid sequence to immunogenic synthetic peptide. The two La Jolla teams in their

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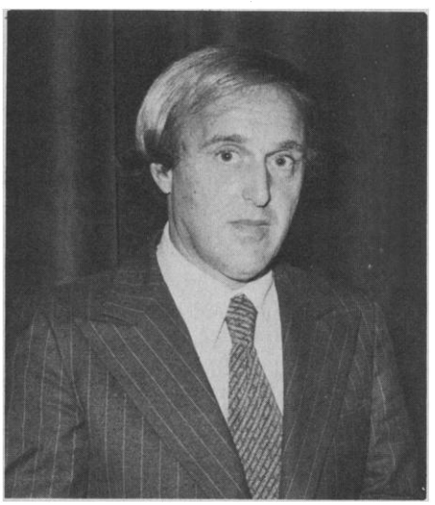
published articles describe only the use of the method as a research tool.*

News of the dispute first began to circulate within the La Jolla research community only this spring, after the prominent public announcements by Scripps of its multimillion-dollar deal with Johnson & Johnson prompted the UCSD/Salk team to explore its patent position as well. The UCSD/Salk team's side of the story is as follows.

According to Russell Doolittle, a protein chemist at UCSD, the idea of the



Molecular biologist Richard Lerner

synthetic antigen approach as a research tool was conceived around October 1978, primarily by Gernot Walter, a virologist then working at the Salk Institute. Walter wanted to distinguish between the different proteins of SV40, a widely studied research virus whose complete DNA sequence had recently become available.

After discussions with Doolittle, Walter synthesized various peptides in Doolittle's laboratory before returning to the University of Freiburg, West Germany, where he is now. He wrote to Doolittle in December 1979 to say that the synthetic antigen approach was working out well.

Some time in early March last year—the exact date is not agreed upon—Doolittle was visited by molecular biologist Richard Lerner and two colleagues from Scripps. Lerner was studying the gene products of another standard laboratory virus, Moloney mouse leukemia virus. Having sequenced part of the virus's RNA, Lerner believed he had found a previously unknown protein. He came to ask Doolittle to run the inferred sequence through his computer bank to see if any similar protein structures were on record.

Doolittle says he told Lerner of the success that his colleague Gernot Walter was having in identifying inferred proteins with the synthetic antigen approach, and suggested that Lerner should do the same. He recommended synthesizing a particular peptide as a probe to see if the unknown protein existed. Lerner said nothing. He continued to visit Doolittle's laboratory on several occasions through the summer and fall to ask Doolittle's help in identifying the antigenic regions of flu and hepatitis viruses.

Walter, Doolittle, and colleagues published their findings about the proteins of SV40 in September 1980. Doolittle says he was "outraged and embarrassed" to read the following month an article in which the Scripps group announced their results with Moloney virus. They had adopted the synthetic antigen approach, and made a peptide very similar to that which Doolittle had recommended. But the Scripps paper, while thanking Doolittle for "helpful discussions," neglected to mention that these included the suggestion of the synthetic antigen method.

Doolittle regards the method as Walter's idea, with his own role having been that of a sounding board and adviser. When the Scripps paper came out, he says, he was seized with remorse at having betrayed his colleague's idea in a way that might allow another group to reap much of the scientific credit for it. Lerner happened to visit his laboratory the next day and Doolittle immediately confronted him, protesting the lack of acknowledgment to Walter.

"All I asked him to do was to write to Gernot Walter to apologize. He said, amazingly, 'I will have to check with my co-authors,' " Doolittle recalls. An hour later, according to Doolittle, Lerner telephoned to say that he had thought of the idea independently, before his first visit in March. Lerner told Doolittle he had found an order slip for a synthetic peptide to be bought commercially, and that the date on the slip was 2 weeks before the March 1980 meeting. In Lerner's view, that proved he had thought of the synthetic antigen approach independently. Doolittle says he asked Lerner why he didn't mention that during the March visit but received "no intelligible reply."

Because of the particular peptide Lerner said was ordered in the purchase form, Doolittle was far from convinced that it proved what Lerner said it did; the peptide was not in fact used as a synthetic antigen, and could have been the basis of a quite different solution to the Scripps group's problem. Nevertheless, Doolittle decided to let the matter slide.

But on 9 March 1981, the San Diego *Union* carried an article describing the Scripps plan to make synthetic vaccines. The article detailed not only the synthetic antigen method but also a way of selecting the antigenic sites of virus proteins, just as Doolittle had been doing for Lerner the previous autumn. "I thought the whole thing would have blown over, but when the San Diego *Union* article came out, which showed these people were going to make a lot of money, that really uncorked the old bottle. The bad manners in science was one thing, but making money out of it was another," Doolittle remarks. Although he believes the work should not be patented, he decided that if Scripps was going to file, so should he and Walter. The University of California patent office is now studying the matter. Walter did about half his work on the technique while at the Salk Institute, but the Salk Institute also declines to discuss what action it may take.

The Scripps side to this story is in outline simple. Lerner says he had the idea first, before learning what the other team was doing, and owes them nothing. The idea of using synthetic antigens came to him in May 1979, Lerner says, during a visit to New York. He was wondering how to identify the proteins produced by cloned brain cell genes. "It was early twilight in Manhattan, and we were walking in Central Park, trying to come up with a solution to this problem," he recalls. Other members of his group were present, since this was just after the annual Cold Spring Harbor meeting on tumor viruses, and an impromptu lab meeting was held to discuss the idea. Since no one had anything to write on, a discarded napkin was found. "We wrote the whole thing down on the napkin," Lerner says.

The brain cell project did not immediately require use of the synthetic antigen approach, but some time in January 1980, Lerner says, he came across another problem. From sequencing the nucleic acid of Moloney virus, the Scripps group found presumptive evidence of a new gene, which they called the R gene. Synthetic antigens seemed a good way to see if the product of the putative gene—the "R protein"—really existed.

Lerner and his colleague Gregor Sutcliffe say they were too busy writing a paper to take up the idea for several weeks. Then in early March, they discussed it with a protein chemist at Scripps, Tony Hugli. Hugli confirms he

*The UCSD/Salk article appeared in the September issue of the *Proceedings of the National Academy of Sciences*, with a received date of 19 June 1980; the Scripps paper was published in the 30 October issue of *Nature*, with a received date of 24 June 1980.

both discussed the general approach (advising them it might not work) and gave them the name of a good peptide synthesizer. He says the discussion took place "sometime in the week before 10 March." It was on 10 March, a Monday, that Lerner says he ordered the synthetic antigen used in his *Nature* article. The first meeting with Doolittle was not until after 10 March, he states.

Lerner and Sutcliffe agree that Doolittle told them, during the March 1980 meeting, of Walter's work with the synthetic antigen approach but stress that Doolittle did not say the experiment had worked. Asked why they didn't tell Doolittle that they were using the same approach, Lerner explains that it would have been "embarrassing and a putdown" for Doolittle to learn that he was not the only one with the idea. They consider that Doolittle has no cause to complain, and they question his motives in doing so.

The concept of synthetic antigens as a research tool is not in itself particularly new. Virologists have been making them at least since 1975. What has given it a new importance is the availability of viral nucleic acid sequences. Both the Scripps and the UCSD/Salk team say they conceived of using the method to verify the existence of proteins inferred from a virus's nucleic acid sequence.

But it is one thing to have an idea; it is another to have sufficient confidence in it to put it into practice. In establishing the independence of the Scripps researchers' approach, two pertinent issues are whether they had the general idea, and whether they had decided to put it into practice, before learning from Doolittle of Walter's experiments.

Lerner's position is that he had the general idea in May 1979, some 10 months before the first meeting with Doolittle. Because of the pending patent application and attorneys' advice, he explains, he has been unable to show *Science* the napkin inscribed in Central Park with the description of the idea.

As for putting the idea into practice, Lerner says his purchase order is proof that he had decided to do so by 10 March 1980. When he first mentioned the purchase order to Doolittle, he said only that it specified a 36-amino-acid peptide or "36-mer." The synthetic antigen used in the *Nature* paper, however, is not the 36-mer but a 15-amino-acid fragment of it. It was for this reason Doolittle found the explanation unsatisfactory. Lerner now explains that both peptides, the 36-mer and the 15-mer, were ordered on 10 March.†

Lerner initially stated that his first meeting with Doolittle did not occur until 3 days later, on 13 March, saying that as evidence he had "a computer search with a date of 13 March in Doolittle's handwriting." Doolittle too originally placed the first meeting at 13 March, but when informed of the date on the computer search, he told *Science* that 13 March must have been the second visit, and that the first visit must have taken place several days earlier. He explains that his practice is to date computer searches with the day of their completion, and that the search performed for Lerner would have taken at least an overnight computer run. Lerner must have come to his laboratory to request the search some time before 13 March, Doolittle believes, and he is "confident" that it was on the first meeting that he told the Scripps group about Walter's work.

Free exchange of information depends upon an unwritten code of behavior among colleagues.

Lerner now concedes that 13 March may have been the second visit but says the first visit was at most 1 day before, and in any event after 10 March. He is sure of this because "We know we got the print-out the same or the next day, because we remember that. No matter how often Doolittle shifts dates, the fact remains that our documentation shows we ordered our 15-mer before we went to see him." Lerner adds that, in any case, it may have been on the second or third visit that Doolittle discussed Walter's work. Asked if the news that a competitor was working on the same approach wouldn't have been memorable enough an occasion to pinpoint exactly, both Lerner and Sutcliffe say that this just wasn't the case. "Scientifically, Doolittle just wasn't that important to us," Lerner explains.

Whatever the value to the Scripps group of the information Doolittle volunteered to them, it is not the priority of the idea but the question of behavior among scientific colleagues that most vexes Doolittle. The issue is important because the free exchange of information and materials among researchers depends upon an unwritten code of behavior among colleagues, a code that is at present being subjected to considerable stress by the commercialization of molecular biology.

The experiment in which the Scripps group put the synthetic antigen method to use underlines the extreme importance to molecular biology of the free exchange of information and scarce materials. To demonstrate the existence of the hypothetical new R protein in Moloney virus, the Scripps researchers obtained from Inder Verma of the Salk Institute a clone containing a DNA copy of the virus's genetic information; they were given unpublished data on the sequence of one of the virus's known proteins by Stephen Oroszlan of the Frederick Cancer Research Center in Maryland; and they received information from Doolittle on the R protein's hypothetical structure as well as news of Walter's experiments. In addition, on a commercial basis, they had peptides synthesized by Peninsula Laboratories.

Yet the acknowledgments given for these various forms of help, though doubtless within the range of accepted standards, were not so explicit as to command universal satisfaction. Oroszlan believes he was fairly acknowledged in the paper, but Verma's donation of the clone is not mentioned. "This has never happened to me before, that someone would take something from me and not acknowledge it. You don't usually get this type of thing written down, but I probably will start doing so now," Verma remarks.‡ As for the synthetic

†Lerner showed *Science* copies of the purchase order documents. A phone quotation from Peninsula Laboratories, dated 10 March 1980, reflects that a 36-amino-acid peptide was ordered from the company at an initial quotation of $7600, which was changed to $8150. Near the 15th amino acid from the C-terminal, the word "stop" is written in an apparently different pen from that with which the sequence of the 36-mer is written.

A recent (26 June 1981) letter from Meikyo Shimizu, director of Peninsula Laboratories, was also made available to *Science*. The letter, addressed to Lerner, states that he ordered the 36-mer on 10 March, and that "At the same time you have asked me to stop synthesis . . . at the 15th residue from the C-terminal." Shimizu told *Science* that, while he is not certain, the addition of the word "stop" probably occurred on the same day.

Lerner's position is that these documents, taken together, prove that the 15-mer was ordered on 10 March.

‡Lerner said that his R protein article indirectly cites, in its references, a clone supplied by Verma, and that this was sufficient acknowledgment. The text of the article, however, refers to data from a new and different clone, and it is the new clone that Verma believes should have been acknowledged. Lerner's response is that the new clone was acknowledged in another article.

peptides, they were bought commercially, so no personal acknowledgment was required, but it is customary to indicate the source of such materials so that others can replicate the experiment. The Scripps group in their article leave the impression that synthesis of the peptides—not a negligible skill—was performed in-house: "We chemically synthesized part of the R protein," they say, whereas in fact a chemist at Peninsula Laboratories did so.

The Scripps group did offer Doolittle a coauthorship on their paper, but emphasize that they did so only on account of the computer search he undertook. They did not tell him the paper described use of the synthetic antigen method, or show him a copy of the manuscript. Doolittle declined the offer, correctly supposing it was just the computer search that they wished to recognize. Whether they should have acknowledged the conversation about Walter's work is a question that depends in part on how much help the information was to them. In favor of an acknowledgment not being necessary is the fact that the information was volunteered, not solicited.

"We think we are fairly generous acknowledgers," comments Lerner. "We are not going to thank Doolittle for an idea he didn't give us. Verma has been abundantly acknowledged—he is a coauthor on two of our papers even though all he did was provide us with two clones. As for the synthetic antigens, peptides can now be synthesized by machine. We designed those peptides and synthesized them in every way except for doing what the machine did."

By not telling Doolittle of their own approach, however, the Scripps group gained an advantage which Doolittle sees as unfair. From that moment, as he puts it, "These people knew they were in a horse race and I didn't. Wherever the idea came from, they knew we would be publishing soon and because of that, their work went astonishingly fast. That was the other thing that gave me pause—how could they have done the work so quickly? As a result, it was very hasty work experimentally, and they got the wrong answer."

Lerner sees nothing remarkable in the speed with which his experiment was conducted. But it does so happen that the experiment is thought by some virologists to be incorrect, at least in its major premise that the R protein of Moloney virus is a new gene product consisting of some 96 amino acid units. "Lerner didn't find anything new; there is no R protein," says Oroszlan. According to

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AID Science Funds Emerge in New Guise

Two years ago Congress voted to establish an Institute for Scientific and Technological Cooperation (ISTC) to foster technological links between the United States and developing countries. But the institute, which was enthusiastically endorsed by prominent members of the scientific establishment, was promptly killed when the Senate refused to appropriate any money for it. Recently, however, elements of ISTC have been resurrected in new guises.

A reorganization under way in the Agency for International Development (AID) will create a new high-level Bureau for Science and Technology, which will administer AID grants to universities in the United States and abroad. It will also be the focal point for coordinating and supporting AID's research and development activities.

The director of the new bureau will be none other than Nyle Brady, the man who was chosen to head ISTC before it foundered in the Senate. Brady, whose nomination is now pending before the Senate, was formerly director of the International Rice Research Institute, the Philippines-based research center that spearheaded the development of high-yielding varieties of rice.

Aficionados of the workings of the foreign aid bureaucracy point out that Brady will rank above other AID bureau chiefs, for he is the only one to hold the title of senior associate administrator.

Another direct descendant of the ISTC proposal is an unprecedented arrangement under which the National Academy of Sciences will receive a $36 million grant from AID to support science and technology in developing countries. About half the grant, which will extend over a 5-year period, will be used to fund research and development projects in developing countries. The arrangement was finalized last January. Funds for the grant are coming from the office of the science adviser to the administrator of AID. When Congress decided not to fund ISTC, it added some $12 million a year to AID's budget for science and technology and gave the science adviser discretion over how the additional money should be spent. The grant to the Academy will account for the bulk of this new fund.

The Academy's program will be conducted by the Board on Science and Technology for International Development (BOSTID). According to John Hurley, BOSTID's deputy director, the funds will be used to support research and development in such areas as nontraditional food crops and fast-growing tree species. BOSTID itself has expressed the need for such studies in past reports to AID.

The grant represents a major new departure for the Academy, and the arrangement was agreed to only after considerable internal discussion in the governing council. For the first time the Academy will be taking on responsibility for managing a large government program, thereby relinquishing some of its vaunted independence from the federal bureaucracy.

—Colin Norman

Triage Applied to British Universities

British universities are digesting the bad news about government funding over the next 3 years. The universities, which depend on the treasury for the bulk of their budgets, face cuts of upwards of 11 percent in operating funds by the 1983–1984 academic year and enrollment reductions of 3 to 5 percent. An estimated 3000 academics could get the sack. Although budgets at all 47 universities will be reduced, the pain will be shared unevenly. Ten institutions face relatively slight cuts. At the other end of the scale, a luckless five will suffer reductions of from 17 to 27.5 percent in annual funding. Most are scheduled for cuts at more or less the average 11-plus percent.

While the universities are publicly financed, the distribution of funds is made by the University Grants Committee (UGC), a peculiarly British institution originally designed to bolster university autonomy. The 20 members of the committee, most of them academics, are appointed by the minister of education. The UGC is technically an advisory committee, but its advice is always followed. Its deliberations are not public, and its members

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Oroszlan and others, the "R protein" is merely a 16-amino-acid peptide, whose general existence was already known, which is cleaved off another viral protein. Lerner agrees the R protein is only a 16 unit peptide after all, but believes that it is a new discovery which could not have been made without the synthetic antigen technology.

Doolittle and Walter won the publication race they didn't know they were in, even though by the narrowest of margins. Modern research being a competitive enterprise, their rivals were doubtless not obliged to tell them of the race, although it surely would have been a friendly act to have done so. Doolittle's belief that Walter's work was not fairly acknowledged is not an unusual event in academic research; scientists frequently feel, with varying degrees of justification, that their colleagues do not cite their work sufficiently. It was for just this reason that Doolittle initially decided to let the matter slip.

Only when Scripps announced it expected to make a lot of money out of the idea did Doolittle protest what he saw as a breach of scientific etiquette. The synthetic antigen case graphically illustrates how tangible a threat commercialization poses to the exchange of information among molecular biologists. "Ideas are a dime a dozen" is a common phrase by which molecular biologists indicate the readiness of their circulation. But when these dime-a-dozen ideas can be converted so quickly into multimillion dollar deals, circulation is likely to be somewhat inhibited, particularly when the etiquette of acknowledging ownership remains subject to different interpretations.

Doolittle has clearly stated the nature of the problem: "There used to be a good, healthy exchange of ideas and information among researchers at UCSD, the Salk Institute and Scripps Clinic. Now we are locking our doors. The threat to scholarship is serious, indeed," he wrote in a letter to the University of California's Board of Patents. Lerner, on the other hand, believes that fears of what commercialization may do to biology have been much exaggerated and that it is in industry's own interest to change academic patterns as little as possible: "Both industry and university people understand that this is a game that must be played by preserving academic values. Good research begets good research regardless of the source of funds. That is why it is counterproductive if people start locking doors against what is an essentially healthy development for everyone," he says.

Simultaneous independent discoveries are by no means rare events in science. What makes the synthetic antigen case unusual is the fact of the interchange between the two laboratories, as well as the remarkable degree of closeness between the Scripps team's decision to put their idea into practice and their being told that their rivals had done so. Given these circumstances, and the commercial value of the idea, an element of controversy may have been inevitable. In such an atmosphere, even small matters can assume significance. A more explicit style of acknowledgment to Doolittle and Walter by the Scripps group might not have averted the dispute, but could not but have helped to reduce friction and to maintain the basis of trust upon which colleagues in academic research freely exchange ideas of all sorts, whether they be worth a farthing or a fortune.—NICHOLAS WADE

Louisiana Puts God into Biology Lessons

The Governor has signed a "creation science" bill, a move that will probably fuel the nationwide creationist fervor

Over the stiff opposition of believers in evolution, a second state in the Union has adopted a law requiring that "creation science" be elaborated in the classroom whenever a science teacher makes mention of Charles Darwin and his century-old and surprisingly controversial theory that links the origin of monkey and man. On 21 July Louisiana Governor David C. Treen signed the "Balanced Treatment" bill into law, saying he had received "hundreds of communications on the subject" and was "not free of doubt" about his decision, but that "academic freedom cannot be harmed by inclusion, only by exclusion of differing points of view."

Up in arms over the law is the local educational establishment. The Louisiana Federation of Teachers says it will file suit, the School Board Association says it is considering the same, and individual instructors are irate. Says Miles Richardson, a professor of anthropology at Louisiana State University who teaches a course on human evolution: "I've already decided in my own mind that I am not going to teach creationism. Instead, I've sent a copy of the bill to the American Civil Liberties Union."

The new high in the creationist tide is significant in two respects. First, in sharp contrast to an Arkansas bill which was passed with little fanfare or discussion in March, the Louisiana bill was vigorously debated by scientists, creationists, and the press before its adoption. The *State Times* of Baton Rouge called it "a confusion of faith and science" and branded the bill as "half-baked." Second, both the Louisiana and Arkansas bills are based on a model bill being circulated around the country by a conservative group in South Carolina, and its adoption by two states is likely to fuel the creationist drive in other legislatures.

The question is whether the bills, which mirror the nationwide tilt to the right and are widely seen by evolutionists as violating the First Amendment separation of church and state, will stand up in court. The American Civil Liberties Union (ACLU) has sued the state of Arkansas over its law in federal court; the trial is scheduled to begin in late October. The ACLU is also considering a lawsuit in Louisiana.

Serving as a peg for much of the creationist fervor is the model bill supplied by the South Carolina group known as Citizens for Fairness in Education. According to Paul Ellwanger, head of the group, 21 states are currently considering creationist legislation, and "the majority of those bills are modeled on ours." He says that many groups have tried and failed to pass their own bills, and that they end up coming to him. "Our bill," he says, "is constitutionally very strong." Ellwanger denies connection with any religious group, an oft-heard statement these days from creationists intent on removing from "creation science" as much metaphysics as

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