the locked Parkfield segment, and toward Carrizo the micro-earthquakes deepen even more before disappearing.

This rough association of rock type, locking depth, and earthquake size intrigues some of Lindh's colleagues. "We would agree with most of this," says seismologist David Oppenheimer of the USGS in Menlo Park. But he, like other seismologists, is frustrated by Lindh's characteristically casual presentation of his idea. So far, Oppenheimer complains, there's been no paper—only a talk drawing on precious little data. "The problem with Al's theory is there's no paper trail we can cite. He's willing to stick his neck out; he likes to stimulate people to think about things. But it's not sufficient to get up in front of a meeting and just talk about it."

Maybe not. But other researchers are already gathering data that is starting to support the model. Seismologists Andrew Michael and Donna Eberhart-Phillips of the USGS in Menlo Park recently probed the structure of California faults using seismic waves crisscrossing the faults from a few hundred nearby earthquakes. As they reported in *Science* (9 August, p. 651), the variations in seismic wave velocity enabled them to trace the varying density of the rocks buried along the fault—something Lindh had only inferred from surface geology. According to the model, the densest rock (the kind most resistant to softening at depth) should go with the largest earthquakes. In their study of five earthquake sites, including Loma Prieta and Parkfield, Michael and Eberhart-Phillips found that the predicted correlation held up well, thus extending it to the kilometer scale at earthquake depths.

These results suggest that Lindh's model might be combined with seismic imaging and other techniques to pinpoint segments of the San Andreas where the rocks are capable of storing up great strain that is due for release. By identifying these most dangerous fault sections and even the parts of those sections most crucial in earthquake initiation, seismologists would gain a new way to focus their search for warning signs of an imminent quake.

Lindh is the first to concede that his idea will need some more testing before it can make much of a contribution to earthquake forecasting. "As we build better three-dimensional models and have more large earthquakes, these ideas will either hang in there or not," says Lindh. But he's not sweating it. Since he recently joined the ranks of the bureaucrats as seismology branch chief at Menlo Park, he jokes that "they can't fire me for having bad scientific ideas." ■ RICHARD A. KERR

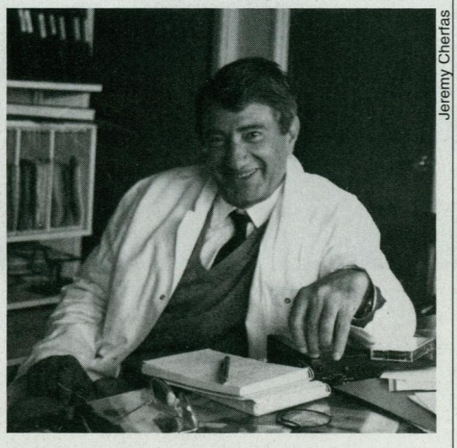
Improvements Seen for RU-486 Abortions

Researchers are working to make the procedure safer but have split over the best way to achieve that goal

Geneva, Switzerland—PERHAPS IT'S a case of absence making the heart grow fonder. In the United States, where doctors have been unable to prescribe RU-486, the controversial French abortion drug has generally been treated, except by anti-abortion groups, as a cause célèbre with no known downsides. Indeed, in the 10 years since its development, RU-486 has been successfully used to induce abortions in 80,000 women, primarily in France. But while it has proved effective when used in association with a prostaglandin, some problems have cropped up.

Mostly these have been relatively minor, such as abdominal cramping, although one feminist group has recently released a report charging that the side effects are worse than they've been made out to be (see accompanying story on p. 199). But three cases of cardiovascular complications—one of them fatal—have been attributed to the RU-486-prostaglandin combination, further fueling opposition to its use by anti-abortion lobbyists. Now comes word, however, that some of the problems are on the way to being solved.

According to new research data obtained by the World Health Organization (WHO) in Switzerland and the drug's inventor, Etienne-Emile Baulieu, professor of biochemistry at the University of Paris Sud, progress has been made on ways to improve the drug regimen used to induce abortions. Still, WHO and Baulieu are far from agreement on where the research priorities should lie.



Jeremy Cherfas

Looking to improve. *Etienne-Emile Baulieu wants safer prostaglandins.*

WHO has been concentrating—with apparent success—on lowering the RU-486 dose. Organization officials have released to *Science* the results of a large clinical trial showing that the dose of RU-486 can be reduced by at least two-thirds without a fall-off in efficacy. But Baulieu says those efforts may be misplaced. Sulprostone, the prostaglandin used in the majority of French RU-486 abortions, is the primary cause, he says, of the chief problem associated with RU-486 use—the abdominal cramps that occur in about 80% of cases. And sulprostone may also be the culprit behind the more serious heart problems that have been reported. Consequently, Baulieu has been spending his energies trying to find a safer substitute—also with apparent success.

The WHO trial included a total of 1188 women who were given the drug in 11 centers in eight countries. At each center, the women were divided into three groups, one of which received 600 milligrams of RU-486, the current standard dose, while the other two received either 400 or 200 milligrams. All got the same dose of prostaglandin. The result? All three RU-486 doses proved equally effective, each producing complete abortions in about 95% ofthe women.

And it may be possible to reduce RU-486 doses even further. According to Paul Van Look who organized the trials at WHO's Human Reproduction Program, preliminary studies have already shown that, using RU-486 alone, doses as low as 150 milligram might be effective. WHO plans to carry out another multicenter trial to verify that observation, using RU-486 with a prostaglandin.

Meanwhile, Baulieu has been making headway in his search for safer prostaglandins. In April, he reported to the French Academy of Sciences results with an oral prostaglandin, misoprostol, widely marketed for the treatment of gastroduodenal ulcer. Given to 100 women, the RU-486-misoprostol combination produced complete abortion in 95 cases, severe pain in only two cases, and no other significant side effects. Larger studies are about to

begin on the combination. Baulieu now says he believes that because misoprostol can be given orally, it could be taken by women in their homes.

Roussel-Uclaf, the company that makes RU-486, is also critical of WHO's studies. "One possibility we would be afraid of," says Arielle Mouttet, head of international marketing for hormones at Roussel-Uclaf, "is a rise in the rate of failed abortions with lower doses of RU-486." Data from 421 women participating in the firm's pre-licensing studies showed that when given without a prostaglandin, 200 milligrams of RU-486 produced complete abortions in only 63% of women against 89% for the 600-milligram dose. Mouttet fears that some women may fail to take the prostaglandin—either because they change their minds after taking RU-486 or because they do not have access to an efficient health care system—and thus run a risk of a life-threatening incomplete abortion.

Van Look defends the WHO's efforts to lower RU-486 doses on the grounds that the smaller the amount of a drug people take the better. "There's no reason why a woman should be given 600 milligrams if 200 milligrams is enough and our findings seem to suggest that it is," he says. Pramilla Senanayake, assistant secretary general of the International Planned Parenthood Federation in London, agrees. "The most important thing is that you are giving a lower dose to the woman," she says.

In the United States, as in the many countries throughout the world where RU-486 continues to be unapproved (the United Kingdom became the second nation to approve its use this July, improvements to the drug combination should boost its acceptability. But science will not be enough; politics is still the key factor in deciding what will happen to RU-486. Following the international uproar that attended the birth of the drug 3 years ago, Roussel-Uclaf now has clear rules about where it will sell the drug: only in countries where abortion is legal, where the social and political climate is favorable to abortion, and where distribution of the drug is tightly controlled.

The company will soon permit the drug to go on sale in Scandinavian countries, where those conditions have been met, and possibly the Netherlands. Third World countries, where 200,000 women now die each year from abortions—often illicit— may follow. Both China (where RU-486 has been licensed) and India could soonbe using the drug. And in efforts to further its availability, Baulieu traveled to Bangladesh at the invitation of the prime minister last week to discuss the introduction of the drug there.

The one country where Roussel-Uclaf says there is no chance of it being introduced is the United States. Mouttet says that her company will not introduce the drug there, despite appeals from the legislatures of New Hampshire and California and the mayor of New York City to provide the drug for clinical trials, because of continuing opposition by abortion foes. ■ JOHN MAURICE

John Maurice is a free-lance writer based in Geneva, Switzerland.

Alcoholism Gene: Coming or Going?

In recent years molecular geneticists have set themselves an extremely difficult task: finding the genes that influence people's susceptibilities to complex diseases, such as cancer and mental illness, that have more than one cause. Just how hard that task is has been driven home once more by a controversy over a proposed alcoholism-susceptibility gene that reached a new pitch with the publication of two conflicting papers in the 2 October issue of the *Journal of the American Medical Association (JAMA)*.

In April of last year, a group headed by Kenneth Blum at the University of Texas Health Science Center in San Antonio kicked off the debate with a report that it had found an association between a marker for one of the brain's dopamine receptor genes and severe cases of alcoholism. Because the receptor is needed for responses of neurons in the brain's "pleasure center," which has been linked to the rewarding properties of alcohol and other drugs, the implication was that a variant in the receptor gene might make a person more vulnerable to compulsive drinking. However, a subsequent study at the National Institute of Mental Health failed to replicate Blum's finding.

Now come the two *JAMA* reports, adding further to the puzzle. In one, a multicenter team headed by medical geneticist David E. Comings of the City of Hope National Medical Center in Duarte, California, not only appears to confirm the connection between Blum's marker and alcoholism, but also links it to a variety of disorders presumed to involve abnormalities in dopaminergic neurotransmission. These include Tourette's syndrome (a tic disorder associated with obsessive-compulsive behaviors), attention deficit hyperactivity disorder, and autism. The researchers found the marker in 42% to 55% of patients with these conditions compared to about 25% of the total control group—and only 15% of a group known to be non-alcoholic. "I strongly believe there is a [common] genetic defect," asserts Comings, although he stresses that he doesn't think the defect causes the diseases—only that it exerts a "modifier" effect.

In the other study, however, psychiatrist Joel Gelernter and his colleagues at the Yale University School of Medicine and the West Haven Veterans Administration Hospital report that they found no significant differences between the occurrence of the marker in a group of 44 alcoholics and 68 controls. "We believe it doesn't increase the risk for anything," says Neil Risch of Yale, one of the study co-authors.

So what's going on here? Somewhat surprisingly, the quarrel in this particular debate is not over the subjects, but over the controls. Both studies found the same frequency of the marker among alcoholics—about 43%. But the Gelernter group also found a similar incidence of the marker in its controls—about 35%—while the Comings group found a significantly lower incidence.

Gelernter believes that a likely explanation for Coming's finding is the "dramatic" variation seen in the marker's prevalence among different ethnic groups. Although all the subjects in both studies were white, neither study included a breakdown of subjects according to ethnic origin, and high-prevalence groups may have been underrepresented in Comings' controls.

Comings doesn't buy Gelernter's argument. He contends that carriers of the marker may have been overrepresented in Gelernter's controls for two reasons: The group was not vetted for alcoholics, and, more important, many controls were drawn from families with a high frequency of Tourette's syndrome. That, says Comings, suggests they are more likely to be carriers of the marker. Gelernter's group counters that members of the Tourette families actually showed a lower frequency than the other controls. Risch adds that removing alcoholics from the controls wouldn't substantially alter the result, since a random population sample can be expected to be no more than 10% alcoholics.

More research will be needed to determine whether the marker that is the object of such feverish interest is a meaningless variation or the sign of a defect with wide-ranging implications. But even if some loose link between the receptor and the diseases eventually proves out, researchers will still be a long way from finding a gene that is specific to alcoholism. ■ CONSTANCE HOLDEN