News
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*** Scientists receive grants for alternatives to animal research.

DALLAS--Millions of women begin each day "putting on their faces." A ritual of applying moisturizers, foundations, eye shadows, mascaras and blushes, the process is as routine as choosing what outfit to wear.

But before these and other body care substances reach the consumer, they must undergo rigid safety tests. Until now testing with animals has been the norm, but new strides utilizing in vitro or "test tube" cell culture techniques are being made to develop alternative methods.

"Alternatives to animal testing are not meant to replace animal research," says James P. McCulley, M.D., chairman of Ophthalmology at The University of Texas Health Science Center at Dallas. "Rather alternative testing will help us become better prepared when we get to the animal testing stage."

McCulley has several grants from local companies to develop alternative testing methods. He is also a member of the advisory board for the Johns Hopkins Center for Alternatives to Animal Testing. He explained that the center was formed several years ago in response to animal rights activist groups who were opposing the "Draize Rabbit Eye Test." The Draize test involved dropping various compounds -- primarily drugs and cosmetics -- into the eyes of rabbits. It was considered by the activist groups to be cruel and unnecessary.

In response to the Draize test and several others, the groups began lobbying and introducing bills into Congress. Their efforts prompted cosmetic and pharmaceutical companies to invest in alternatives to animal research. The Johns Hopkins Center is funded by this kind of outside contribution.

Politically, McCulley says, efforts to develop alternatives are still very much in the congressional picture. An animal welfare bill, HR 6828, "The Humane Treatment and Development of Substitutes for Animals in Research Act, "was introduced to the House last session. It never received floor consideration.

Another animal bill was introduced in the Senate but opposition kept it too from reaching the floor. However, hearings are expected to be held on these issues in the new Congress.

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Clearly, McCulley says, the political climate is calling for alternative testing methods. Scientifically, he says, the capabilities do exist for developing alternatives. There are two major areas of alternative research currently being studied: the in vitro tissue culture approach of growing living cells in cultures and testing the effects of substances on these cells, and mathematical modeling or Quantitative Structure Activity Relationships, QSAR.

"The tissue culture approach is where the major thrust is," McCulley says, "but it is possible that QSAR will someday be used in combination with this.

"What one does with QSAR is to look at known phenomena and mathematically try to predict the different cause-and-effect relationships. Rather than getting a hundred points on a curve, one can get several points on a curve and then, by mathematical modeling, predict the final outcome. But one does have to have the real points to prove the modeling is correct. It is conceivable that these real points could be determined, at least in part, through tissue culture tests and follow-up animal research."

McCulley and Steven Pakes, D.V.M., Ph.D., director of the Animal Resources Center at the health science center, share a grant from Mary Kay Cosmetics of Dallas to develop and test in vitro tissue culture lines of the corneal epithelium or outer layer of the cornea. McCulley also has a grant with ALCON, a pharmaceutical company in Fort Worth, to test the effects of a new drug on corneal endothelial cells grown in vitro. Corneal endothelial cells make up the inner lining of the eye.

"At present with Mary Kay, we are establishing a system but not testing a substance. We have successfully developed tissue culture lines of corneal epithelium. Now we want to use those tissue culture cells as targets to evaluate toxic effects of compounds," McCulley explains.

"Some of the things we have to know are: what are the appropriate indicators of toxicity? Or, what indicator or battery of tests will predict toxicity? The tests may vary depending on the compound and the route of administration of the compound. From the cosmetics industry standpoint, most likely we'd be looking at surface cells.

"I think what will happen with time is that we will define a battery of tests. We'll use these tests to screen for toxic substances. If a compound gets through this critical battery of tests, then it is not apt to be toxic. It would be at this stage that we would go to animal research to substantiate our cell culture findings."

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Why hasn't this kind of system been in use before now? Scientifically, McCulley explains, it has only been in the last five to 10 years that cell culturing has become sophisticated enough to enable researchers to grow a wide variety of cells in culture. Politically, he says, the regulatory agencies like the Food and Drug Administration (FDA) have to be convinced that the tests are credible.

Woodring Wright,M.D., Ph.D., assistant professor of Cell Biology and the person in charge of the UTHSCD Cell Culture Registry, explained the history of growing cells in vitro and why the timing is right for developing new cell lines and testing approaches.

Wright says that cell culturing has traditionally been hampered by the scientist's inability to reproduce the natural environments that specific cells grow in. "Two factors are involved," Wright explained. "First, the kind of cell one is trying to culture is important, and second, the media (the chemical base that the cells are grown in), has to mimic the natural environment with a good deal of precision. "In many cases, Wright says the natural environment may consist of 30 to 40 different components.

In terms of cell types, he says there are essentially two kinds: differentiated cells and undifferentiated cells. "The differentiated cells are very specific and are the ones we are most interested in, in terms of cell culturing for alternative testing methods. These cells are from specific tissue sites and continue to express the same functions," Wright explains. "Undifferentiated cells are found throughout the body and are not specific to any one site."

Differentiated cells must have very specific media in which to grow. Corneal epithelium and endothelium are good examples of differentiated cells.

"It is interesting that some of the first cell lines developed - HeLa and L cells are the most famous - were both vigorously growing undifferentiated tumor cells," says Wright. "The HeLa type was successfully cultured in 1952 from the cervical carcinoma of a young woman named Henrietta Lacks. The L type is from a mouse cell line. Most of our media formulas were initially developed for the growth of these tumor cells. So it's not suprising that the components of the media had to be revised in order to grow differentiated cells."

Because of the difficulty of cultivating differentiated cells, Wright recently organized a tissue culture registry at the health science center. "We have a lot of researchers working with differentiated cells, and it is very valuable to know who is working on what. The registry will hopefully cut down on some duplication of effort and let us know how broad our base of differentiated cell types is."

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The prospect of combining tissue culture research with animal research will allow researchers greater latitude when choosing how they will carry out an experiment, Pakes predicts.

"It will give us one more way of making a 'conscious decision' in terms of how experiments can best be conducted.

"All research grants that require animal use as part of their protocol are currently reviewed at our institution by an animal resources committee. The committee may approve the grant or it may make suggestions concerning the testing methods. These suggestions can lead to a change in the project approach," says Pakes.

"It is conceivable that, as tissue culturing becomes more and more feasible, we will look toward it as a possibility when reviewing grant proposals. Our animal research has always been very focused, very thoughtful and very purposeful. We see this as an another way of maintaining those standards."

How soon tissue culturing will be ready for alternative testing purposes is not known. "We're really just beginning our work in this area," McCulley said. "While we already have some in vitro tests, these still need to be validated. Then the next step is getting approval by federal regulating agencies.

"The Center for Alternatives to Animal Research at Hopkins is only a few years old. We are just beginning to explore the possibilities for studies both at the center and throughout the country," he explained. The Hopkins center funds projects internally and at other institutions. It is a source that researchers interested in conducting alternative studies can turn to for funding.

McCulley says that, while the benefits for this kind of research are real, there are some fears in the scientific community. "The negative side is the risk of overreaction on the part of the government. It is feared that the National Institutes of Health (NIH) will have a major set-aside of funds for development of alternatives to animal research, leaving less funds for other research interests.

"Of course, the other side of the coin is that it has also put pressure on outside industry to develop alternatives. Their steps in funding research and supporting the Center for Alternatives to Animal Testing will hopefully balance things out."

But, McCulley reiterates, the major thrust here is not economics. "The major thrust is that it is an appropriate step forward in science at this time, and it is a positive move in terms of the animal rights concern."

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