

## The pill: Confusion over cancer issue

Recent research results tend to complicate, rather than clarify, any possible relationship between oral contraceptives and cancer.

In late October the British Government released the results of a six-year animal study looking for a possible causative link between various oral contraceptives and breast and uterine cancer. Rats and mice were given estrogen-progestin (progesterone) products that have been marketed in Britain and the United States. The rodents were also given some all-progestin products that have been marketed in Britain but not in the United States. All test products were given to the rodents in dosages, adjusted for body weight, 200 to 400 times what a woman would take.

With the exception of several estrogen-progestin products, the products produced no breast or uterine cancer. The estrogen, rather than the progestin, in these products was deemed to be the cancer-causer. The British Commit-

tee on Safety in Medicines concluded that these birth control pills probably do not present a peril at the dosage levels women take them. It cautioned, nonetheless, that women on the pill should be watched for breast cancer.

A U.S. Food and Drug Administration spokesman says that the FDA does not question the results of the British study. But he points out that the FDA does differ from the British in its emphasis on animal models. The British have tended to put more weight on rodent studies, the FDA on dog studies.

Several years ago the FDA also found that birth control pills could, when given in dosages several hundred times larger than the human dose, cause breast and uterine cancer among rodents. Because rats are prone to mammary cancer, and certain strains of mice are susceptible to cancer induced by a number of chemicals, the FDA was reluctant to take any action based on these results. Meanwhile, though, studies were showing that several all-pro-

gestin compounds that had not yet been approved for marketing could cause breast cancer or breast nodules in dogs. On the basis of these results, the FDA ordered that all clinical studies with the products be terminated. The products were not allowed to be marketed.

Women who were taking the products in the since-terminated experiments have been followed up for signs of breast cancer. None of them have been diagnosed as having it. Consequently the FDA has received some criticism for passing judgment on the basis of too-sensitive animal models (dogs). Yet the FDA does require that all potential birth control agents be tested for cancer-causing ability on rodents and monkeys as well as dogs. "All birth control pills on the American market," the FDA spokesman asserts, "were clean in dog and monkey studies, and their effects in rats and mice could be considered safe—as far as safety goes. Everything is relative."

If British and American differences over what animal models should be used confuses the pill-cancer causation issue, various studies sponsored by the National Institutes of Health fog the issue even more. According to John Schrogie, an NIH authority on the pill and cancer, NIH clinical studies suggest there is no particular link between breast cancer and oral contraceptives.

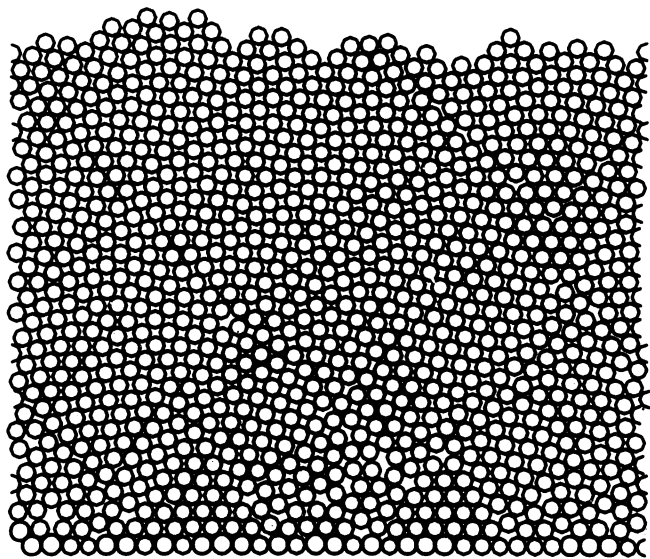
### Packing spheres by computer

The ability of computers to spare human beings arduous calculational toil increasingly recommends them for use on all manner of problems. Suppose, for example, one wanted to know how several thousand balls dropped at random into a box would stack.

This is known as the sphere-packing problem, and William M. Visscher and M. Bolsterli of the Los Alamos Scientific Laboratory define it as: "Given spheres with radii distributed according to a prescribed probability density, and given that they are packed together randomly by some rule to be specified, what is the nature of the resultant heap?" The problem has applications in many fields of science including metallurgy, ceramics, soil science, biology, physics and chemistry. Visscher and Bolsterli have worked out a computer simulation of the problem in two dimensions (heaps of hoops) and three dimensions in the case where the balls are acted upon by the force of gravity.

Among the new things they found was a kind of domain structure in two-dimensional packing. The effect appears when hoops of a certain diameter are dropped onto a base layer of slightly larger hoops. After an initial mixed-up portion near the bottom, the hoops arrange themselves in square domains tipped 45 degrees from the vertical.

To test their three-dimensional code, Visscher and Bolsterli tried to generate what is called a hexagonal close packed array (an arrangement that occurs in many crystals). They found that if they used balls of uniform size on a base of very slightly larger balls, they could generate an h.c.p. pattern if the base layer were laid out in a hexagonal array. When they tried dropping balls of dif-



Visscher and Bolsterli/Oct. 27 Nature

*A two-dimensional stack exhibiting square domains.*

ferent sizes (such as might result from errors in machining) on a uniform hexagonal base, they found that the h.c.p. pattern was destroyed after seven or eight layers.

The work is a beginning rather than an end. Although the code will take any distribution, the calculations were limited (for reasons of memory and time) to less than 10,000 balls. This is not yet statistically good enough to simulate an array of interest to ceramicists or metallurgists.