

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.

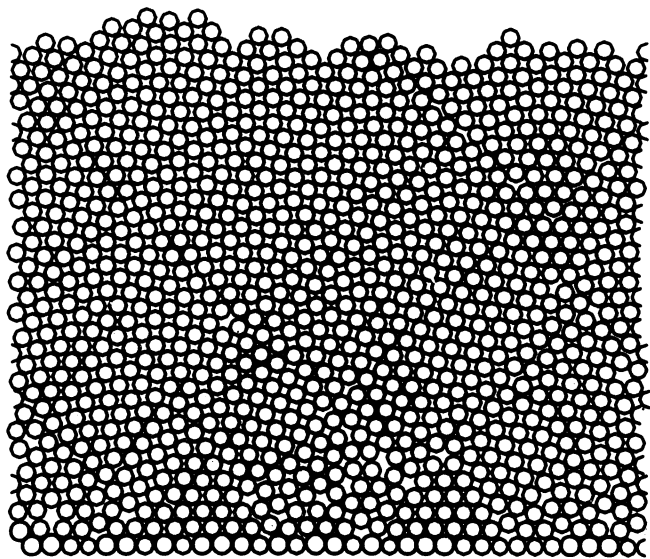
Packing spheres by computer

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.

But they indicate that oral contraceptives, along with sexual relationships early in life, sexual promiscuity and pregnancy, may heighten the risks of uterine cancer. The NIH is now launching a study of 30,000 women in 10 regions to sort out these risks.

Even more muddling is mounting evidence that oral contraceptives may prevent breast and uterine cancer. At a meeting last week in Washington of the International Confederation of Midwives, R. T. Ravenholt of the Agency for International Development described some of this evidence. In the United States, where oral contraceptives were first introduced and used in large measures, mortality rates for cancer of the uterus have decreased rapidly and progressively during the first decade of pill use, especially among younger women. Several clinical-epidemiological studies show women with breast tumors, both benign and malignant, to have had less prior experience with oral contraceptives than matched control patients without such disease. One of the largest and most recent of these studies is reported by Martin P. Vessey and Richard Doll of Oxford University, England, in the Sept. 23 *BRITISH MEDICAL JOURNAL*.

Obviously even a "miracle drug" like the birth control pill would be hard put to both cause *and* prevent breast and cervical cancer in women. Douglas Janss of the National Cancer Institute says the situation is not as hopeless as it seems. One problem, he says, is that investigators have used different animal models with different sensitivities to cancer, which may or may not approximate human sensitivity to cancer. Another is that they have used closely related hormones, like the estrogen class, with subtle, yet divergent biochemical specificities in target tissue. And the studies have used diverse, not-always-comparable approaches. The only way to obtain a conclusive answer to the question of whether the pill can cause or prevent cancer in humans, he declares, is to design better programs for testing compounds in animals and patients. The NCI is presently working up such programs. □

MMPI questions

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Stonehenge: A calendar or just a crematorium?

Between 2000 and 1500 B.C. an impressive ceremonial temple—Stonehenge—was erected in Great Britain. Archaeological reconstruction of the site shows that the monument consisted of a circle of immense, finely tooled stone archways surrounded by a ring of 56 equally spaced Aubrey holes (named for their modern discoverer). Looking out from the center of Stonehenge, the Heel Stone can be seen. It marks on the horizon the point of sunrise at the summer solstice. This fact, and the precisely proportioned placement of the stones and holes, has led archaeologists to presume that the monument had some great astrological significance to its Neolithic architects.

In 1963 Gerald S. Hawkins of Boston University and the Harvard-Smithsonian Observatory suggested that the Aubrey holes provided a system for counting the years of a 56-year cycle of eclipses. "Perhaps," he said, "cremations were performed in a particular hole during the course of the year, or perhaps the hole was marked by a movable stone."

Now Robert R. Newton and Robert E. Jenkins of the Applied Physics Laboratory of Johns Hopkins University in Silver Spring, Md., say the Aubrey holes were probably used to count months, not years, if they were used as counters at all.

The physicists arrived at this conclusion as an off-shoot of a project in which they were attempting to predict the orbits of manmade satellites. One method of verifying such data is to apply it to the moon and then predict backward and check the results against ancient observations of lunar and solar eclipses. Doing so, the researchers found a 111- or 112-month cycle coinciding with the position of the setting of the summer new moon. They explain in the Oct. 27 *NATURE* that the Stonehengers "could easily have made these

predictions with the use of a counting circle of 111 holes. If they preferred not to build a circle with this many holes, they could have used a circle of 56 holes just as easily." Two times around the circle would predict the summer new moon.

Jenkins says the lunar calendar is more likely than the eclipse predictor, but admits that it is just as speculative a hypothesis. "In fact," he says, "we are starting to conclude that you could find support for or against almost any theory." The Heel Stone may have been used to mark the summer solstice but the Aubrey holes may have no astrological significance at all. As an alternate explanation, the researchers say perhaps there were 56 families, clans or social units who built Stonehenge and who were entitled to dig one of the Aubrey holes and use it to inter cremated remains. □

Glomar's Leg 26 finds old Indian Ocean sediments

Scientists on Leg 26 of the Deep Sea Drilling Project have returned to port with the oldest sediments yet recovered from the Indian Ocean, evidence about the identity of a suspected continental fragment and an outline of the history of two ridges.

The Glomar Challenger docked at Fremantle, Australia, Oct. 30 after a two-month, 5,580-mile excursion through the Indian Ocean. The ship left Durban, South Africa, Sept. 6 and its scientists drilled at nine of the ten sites planned.

The Leg 26 researchers, led by Bruce Luyendyk of Woods Hole Oceanographic Institution and Thomas A. Davies of Scripps Institution of Oceanography, drilled at two sites in the Wharton basin, west of Australia. One produced sediments 101 million years old. The other site, farther south, contained even older sediments—105 million years. On the Naturaliste Plateau southwest of Australia they found sedi-