

Drug firm and FDA suspend IUD sales

A growing number of reports of death and injury associated with the use of the Dalkon Shield, an intrauterine contraceptive device, has caused the manufacturer to suspend sales and distribution until a Food and Drug Administration advisory committee decides on its safety. FDA Commissioner Alexander M. Schmidt is also recommending that doctors not make additional Dalkon Shield insertions until the safety questions are answered.

Seven women have died from infected spontaneous abortion (miscarriage) while using the device, and more than 100 nonfatal cases have been reported. Most of the infections occurred during the mid-trimester of pregnancy. The manufacturer, A. H. Robins Co., of Richmond, Va., has received an increasing stream of reports since they issued a "Dear Doctor" letter in May, cautioning physicians about the possible complications if a patient should become pregnant while using the device.

The FDA Obstetrics and Gynecology Advisory Committee, a group of physicians that meets several times yearly to make decisions and recommendations on drugs, devices and medical practices, met June 11 and 15 to hear testimony on the Dalkon Shield. A. H. Robins representative Frederick A. Clark Jr., told the panel that doctors' reports have often been incomplete and inaccurate, and that the device "should not be hastily judged." He said "it is hard to believe" infection could occur with the IUD sitting high in the uterus, and that only low lying IUD's (displaced accidentally or by the wearer herself) would facilitate infection.

A team of FDA physicians from the Center for Disease Control in Atlanta, presented preliminary data behind closed doors. Those data will not be released until August 21 when the Obstetrics and Gynecology Advisory Committee will meet to make final recommendations to Schmidt.

The Dalkon Shield has been inserted in more than 2.2 million American women, and about a million women in 41 foreign countries. The device's effectiveness has also been questioned; an unpublished British study reports a 3.6 percent pregnancy rate in second year users, but a researcher from Beth Israel Hospital in Boston, Johanna Perlmutter, reported a pregnancy rate of 18.5 percent.

The FDA says it will advise physicians through the FDA DRUG BULLETIN about the precautions to be taken in women who become pregnant while using the Dalkon Shield—removal of the device, or possible therapeutic abortion if removal could not be readily accom-



plished. The DRUG BULLETIN will also carry a request for doctors to report all adverse IUD reactions to the FDA. □

Inheritance and high cholesterol

There are different causes for high cholesterol in the blood. One is inheritance. One form of inherited high cholesterol is familial hypercholesterolemia. One in every million persons is a homozygote for this disorder, that is, has received the dominant high-cholesterol gene from both parents. Having a double dose of the gene, the homozygote has six times more cholesterol in his blood than a healthy person and often succumbs to a heart attack before age 20. One in every 500 persons is a heterozygote for this disorder, that is, has received the high-cholesterol gene from only one parent. The heterozygote has two to three times more cholesterol in his blood than a healthy person. He often has a heart attack around the age of 40.

An explanation for why homozygotes have a six times elevation and why heterozygotes have a two to three times elevation is reported in the July 5 SCIENCE by Michael S. Brown and Joseph L. Goldstein, internists at the University of Texas Southwestern Medical School in Dallas.

During the past year or two, Brown and Goldstein have learned that cells called fibroblasts have receptors on them that bind with cholesterol-lipoprotein complexes in the blood. When the complexes bind to the receptors, an enzyme that regulates the rate of cholesterol synthesis is turned off. Then cholesterol production is arrested, until the complexes have dwindled enough in the blood to switch cholesterol synthesis back on.

Brown and Goldstein now report in SCIENCE, that homozygote fibroblasts were able to bind with cholesterol-lipoprotein complexes with about 3.6 percent efficiency of normal fibroblasts. Heterozygote fibroblasts were able to bind with the complexes with about 40 percent normal efficiency. Both homozygote and heterozygote fibroblasts were not deficient in their ability to bind to the complexes, rather, they were deficient in their number of receptor molecules. The heterozygote fibroblasts were able to show 40 percent binding efficiency because they had received a number of normal receptor molecules from the normal cholesterol gene inherited from one parent.

These findings suggest why homozygotes have a sixfold elevation in cholesterol, whereas the heterozygotes have only a two- to threefold elevation. Since cholesterol-lipoprotein complexes are crucial in the feedback regulation of cholesterol synthesis, they have to build up in the blood in order to bind to receptors and thereby turn off cholesterol synthesis. But the fewer receptor molecules there are, the more cholesterol has to build up in order to bind to the molecules and switch off synthesis. That's why a 96.4 percent reduction in receptor molecules on homozygote fibroblasts could well lead to a sixfold rise in cholesterol complexes in the blood, and why a 60 percent reduction in molecules on heterozygote fibroblasts could lead to a two- to threefold rise in cholesterol. □

Soyuz practices for co-op mission

For many months, U.S. and Soviet working groups have been shuttling back and forth coordinating details for next summer's international space spectacular, the Apollo-Soyuz rendezvous in orbit. Last week, cosmonauts Pavel Popovich (veteran of the Vostok 4 flight in 1962) and Yuri Artyukhin (making his first flight after 11 years as a cosmonaut) took off toward a rendezvous with a previously-launched Salyut space station—the first Soviet docking practice since the Soyuz was redesigned following the deaths of three cosmonauts from a pressure leak during the landing of Soyuz 11 in 1971.

The changes made to the Soyuz design were not concerned with docking procedures; they were primarily to refit the spacecraft for use by two cosmonauts in spacesuits as protection against depressurization, rather than by three in shirtsleeves. Nonetheless, docking will be a critical part of the Apollo-Soyuz exercise. An adapter carried by

the Apollo will enable the two ships to mate, after which the crewmen will take turns transferring back and forth between spacecraft.

For the rendezvous, the Soviet craft will be the "passive partner" as the Apollo crew flies to it and performs the coupling operation. The two countries' spacecraft, however, apparently use fundamentally different techniques for the approach to within rendezvous distance. The Apollo style is for the astronauts to fly the whole approach themselves, aided by guidance information radioed up from the ground. In last week's Soyuz 14 rendezvous, however, the Soviet news agency Tass reports that with a kilometer to go before docking, "an automatic approach complex went into play," with the cosmonauts resuming control for the last 100 meters.

Once aboard the space station, they began a variety of tasks including biomedical and earth resources studies, while below in the Soviet Union, a NASA working group was concluding another visit in preparation for the joint mission. □

Watergate spillover in science agencies

Probably it was inevitable: The political barbarism of Watergate has finally spread its taint to the scientific community. Appropriately enough, the news came in a "leak," to *SCIENCE* magazine, of a draft report by the Senate Watergate Committee staff describing a White House plan to use grants, contracts and appointments in Federal science agencies to gain political advantage. But because of limited time and their own set of priorities, the committee did not investigate possible science agency improprieties with the same vigor they used in pursuing those of other agencies, remarking that the Congressional committees having oversight over those agencies should take up the matter.

The scheme—euphemistically called the "responsiveness program"—apparently originated in the year preceding the last election with the then special assistant to the President, Frederic V. Malek, now deputy director of the powerful Office of Management and

Budget. In a memo outlining the plan, Malek cited initial successes in rechanneling Department of Commerce funds for political benefit, but groused that the total amount so far only added up to about a million dollars when perhaps \$1.4 billion "could be redirected in some manner" over the next two years. He ended the memo with the admonition that agencies should be reminded that the program had "the President's full backing."

Malek specifically mentions the National Oceanic and Atmospheric Administration (NOAA) as a target agency (though he called it by the wrong name) and another White House aide, Peter Millspaugh, nominated the National Science Foundation (NSF), but the Senate committee did not pursue these two leads to see if either of these agencies were actually used in the responsiveness program. The committee did, however, investigate two other science-related agencies, the Occupational Safety and Health Administration (OSHA) and the Urban Mass Transportation Administration (UMTA), and the results are not reassuring.

OSHA is responsible for promulgating health and safety standards for industries, and in 1972, the then assistant secretary of labor for OSHA, George C. Guenther, outlined how his organization could be used as "a sales point for fund raising and general support by employers." As a result, according to Senate testimony by his boss, Lawrence Silberman, publication of certain safety standards was withheld until after the election.

UMTA represents the R&D arm of the Department of Transportation, in matters of mass transit. The agency head in 1972 was Carlos V. Villarreal, one of the highest ranking Spanish-speaking political appointees in the Government, who served as a key Presidential spokesman, according to *SCIENCE*. The Senate committee turned up evidence, mostly in the form of memos, that Villarreal met frequently with White House representatives to discuss grants and that these discussions led to grants and contracts for friendly businesses. (One memo notes setting aside \$300,000 for one of "our" Spanish-speaking contractors).

Using public office to interfere with a Presidential campaign violates the Hatch Act and awarding grants on the basis of personal or political gain is a felony of ancient lineage. The next question is whether or not other appropriate investigative bodies will pursue some of the leads uncovered in this latest aspect of the seemingly endless Watergate squalor. □

Antifertility agent receptors found

Prostaglandins, a family of chemical compounds which affect virtually all body tissues and organs (SN: 10/10/70, p. 306), are known to be antifertility agents. They are being studied intensively in an effort to unravel the mechanism by which they affect the reproductive organs, and now another step has been taken toward understanding them.

Two scientists from the fertility research unit of the Upjohn Co. in Kalamazoo, Mich., Alan E. Wakeling and Lillian J. Wyngarden, present evidence in the July *ENDOCRINOLOGY* on the existence of prostaglandin receptors in human, monkey and hamster uteri.

Expanding on their previous work with broken-cell preparations of hamster uterine tissue, they used cultured tissue slices of hamster, monkey and human uteri. Myometrium (the muscular uterine wall) and endometrium (the mucus uterine lining) tissues were incubated in the presence of different levels of radioactively labeled E- and F-type prostaglandins. Analysis of the uptake revealed that "prostaglandin receptors are present in the [hamster], monkey and human myometrium."

A co-worker at Upjohn, Frances Kimball, says that the results were "not unexpected. The prostaglandins induce abortion by causing myometrial contractions. Any compound that does that will cause the loss of the fetus, placenta or both." It is logical, she says, that receptors should be found in the af-

ected tissue. Previous work by Wakeling and Wyngarden showed hamster receptors to be partly protein, and probably located in the small particle fraction of the cell.

Another portion of the current project, Kimball points out, was to "see if the steroids estrogen and progesterone that occur during the estrous cycle, influence the action of the prostaglandins. It had been suggested that cramping of the uterus during menstruation might be caused by prostaglandins, and that the increase in estrogen before menstruation might increase the number of receptor sites and lead to the cramping."

To test this, the researchers monitored the specific binding of prostaglandins in the hamster uterus during different stages of the estrous cycle, during pregnancy and during exposure to levels of progesterone and estradiol (the primary estrogen produced by the ovary). They found that variations in the uptake of prostaglandins did occur and "may be related to the levels of ovarian steroids." Kimball said, "It would probably be out of order to draw conclusions about the increase in binding sites without further research."

Synthetic prostaglandin drugs are now being used as abortion-inducing agents during the mid-trimester of pregnancy. They can be used to induce contractions and are "safer, cheaper and more efficient than salination," Kimball said. □