More fuel for the pill controversy

The shelving of two birth control pills associated with breast nodules in beagles raises questions about test procedures

by Barbara J. Culliton

Last month, in a move described as a "course of extra caution," two of the largest drug houses in the United States pulled their birth control pills off the market. The Upjohn Co. of Kalamazoo, Mich., announced the withdrawal of its combination pill, Provest, and Eli Lilly and Co. of Indianapolis announced it will no longer sell its sequential product, C-Quens.

The action of the two companies, commended by Food and Drug Administration Commissioner Charles C. Edwards as the only prudent course, adds perplexing new dimensions to the pill controversy. It not only places one more item in the minus column in the tally of pros and cons of oral contraception but also brings into the open a smoldering argument about the validity of existing procedures for evaluating pill safety.

In accord with FDA requirements, manufacturers have been monitoring, and are continuing to monitor, the effects of oral contraceptives in long-term studies on dogs and monkeys. (Nine companies produce some 30 different birth control pills.) It was from such tests, conducted during the past year and a half, that Upjohn and Lilly scientists concluded that a disproportionately high incidence of breast nodules developed in young beagles.

None of the nodules was cancerous. Nevertheless, on the grounds that the nodules in beagles may be predictive of what could happen to some women and that, malignant or not, breast nodules are undesirable, Provest and C-Quens have been shelved.

The question now being discussed in scientific circles is whether beagles, or any dogs, are, in fact, suitable animals for such studies and whether they are good indicators of what could occur in women. In an effort to get an official review of the issue, Syntex, the California company which manufactures a number of oral contraceptives and which supplied Lilly with one of the primary ingredients in C-Quens, has turned to the Department of Health, Education and Welfare. In a letter to Dr. Roger O. Egeberg, Assistant Secretary for Health and Scientific Affairs, Syntex scientists have asked HEW to request the National Academy of Sciences to appoint a panel to "evaluate the relevance of tests on beagles and render a public report." There has been no reply from HEW thus far.

Objections to using beagles as experimental subjects in oral contraceptive studies rest on three points. To begin with, there are no scientific grounds for selecting these animals in the first place. Beagles are used, in the words of one FDA authority, simply "because they are there." They are traditional, docile, easy to handle and available. Declaring that this hardly constitutes sound scientific practice, objectors argue that beagles are a poor choice because they are known to be highly prone to spontaneous development of breast nodules and because they tend to be roly-poly, obese animals with more than the average amount of body fat in which to store drug products. A further objection is that beagles have a biannual estrous cycle which is markedly stepped-up when they are given daily doses of estrogen and progesterone, the hormones in birth control pills. By merely giving them oral contraceptives, scientists are disrupting their normal reproductive cycles in a severe fashion that is not comparable to what happens in women.

While the beagle debate continues unresolved, there is general agreement that observations in rhesus monkeys, closer to man in the evolutionary scheme, are pertinent. Dr. Victor Berliner, an FDA pathologist, observes that these animals have reproductive systems analogous to human beings and that their incidence of spontaneous breast nodules or frank tumors is extremely low. Thus, if nodules do develop in rhesus monkeys in drug trials it is possible to presume a direct link between the abnormal growth and the experimental agent.

So far, neither Provest nor C-Quens, nor any other birth control pill on the market, has induced nodules in monkeys. Nor is there any evidence linking the contraceptives to nodules or tumors in women, though, as Dr. Roy Hertz of the Population Council in New York points out, it will take 10 years or more of experience before scientists can expect to get any data on this score one way or the other. If there is any association between the pill and cancer, he comments, it will be the mid-1970's before it shows up.

Whether in the course of time contraceptives other than Provest and C-Quens will be implicated in the induction of nodules in beagles is something scientists are unwilling to predict, though Commissioner Edwards stresses that there is no cause for alarm among pill-takers.

Both Provest and C-Quens contain a progesterone component unlike that in other marketed products. In Provest, which had about two percent of the oral contraceptive market, the progesterone is medroxyprogesterone; in C-Quens, accounting for 7.5 percent of the market, it is Syntex-supplied chlormadinone. These two compounds are similar; they both differ from other progesterones in their molecular structure and biologic activity. Says one Upjohn scientist: "Medroxyprogesterone and chlormadinone are straight progesterones, as pure as motherhood itself. Other progesterones have estrogenic activity."

It is ironic that breast nodules developed in animals taking drugs with such a pure progesterone component. The prevailing hypothesis is that if oral contraceptives do have any relation to cancer, it is probably the estrogen which is responsible. An explanation remains to be found.

In any case, these developments, along with evidence reported last January that beagles taking the Syntex experimental, progesterone-only minipill developed nodules (SN: 1/24, p. 93), cast a pall on the hope that the perfection of such mini-pills would constitute a way around the estrogen-cancer issue.

Unfortunately, according to Dr. Hertz, evidence linking progesterone to breast nodules, rather than exonerating estrogen, merely complicates the picture.

"We know," he says, "that in the rat, mouse and rabbit, estrogen is carcinogenic. It is probably not so in the dog; at least not as far as we can tell. In its response to pure progesterones, the dog has behaved in an unexpected way, and we know nothing of the monkey yet. The dog may metabolize progesterone differently than human beings."

Evaluating the total picture, Dr. Hertz says simply, "It is very confusing." No one disagrees. □