

tal where there is a reporting system of extraordinary quality. It has been made easy to follow by providing staff physicians with reporting cards attached to the patients' charts.

Dr. Leighton Cluff, professor of medicine at Johns Hopkins, and three Public Health Service epidemiologists made daily inquiries of doctors and nurses about drug reactions in a 120-bed medical service. They found that those supposed to fill out the cards failed so often that fewer cards were filled out for reactions in the entire hospital than the survey found had actually occurred in a 10 per cent sample of the hospital.

ENTHUSIASTS TROUBLED

If the 10,000 adverse reactions are a shaky foundation for judgments on safety, so are the uncontrolled studies upon which so much reliance has been placed to date. The studies have troubled even such exuberant boosters of the pills as Dr. Joseph Goldzieher ("I can think of no condition in which these pills would not be safe to take").

Citing the "deficiencies in published trials" in an article in the *Medical Journal of Australia* last June, he said that "much of the current discussion of the incidence of side effects is an exercise in futility."

In the *British Medical Journal*, Dr. Geoffrey Rivett said he had found no circulatory disorders in between 50 and 100 patients on the pills, even though some of them had a history of such afflictions.

"But such figures prove nothing," he said. "It would be a great help if an authoritative body would carry out" a valid trial. (See accompanying box.)

The FDA's Wright committee did not carry out a valid trial. Its mission was to determine if the incidence of thromboembolic phenomena—clots in the bloodways—is significantly higher in women on the pills than in women in the normal population 15 to 45 years old.

The committee found it impossible to get solid, usable data out of cases of nonfatal clots in Enovid users as recorded in the files of FDA and the manufacturer.

For that reason, the committee could shed no light on the incidence of a condition that is nonfatal but can cause lifelong disability.

The committee concentrated on fatalities, for which the data were more complete. Even so, the consultants labored under terrific handicaps.

The rate of side effects is the product of a fraction. The numerator is the estimated number of persons in whom adverse effects have been reported. The denominator is the population estimated to have taken the drug being studied.

If for any reason the numerator is too small or the denominator too large, or if both flaws exist, the incidence is understated.

To determine the incidence in the normal female population, the committee divided the population believed to be at risk—the denominator—into the number of cases of fatal lung clots as reported in death certificates for 1962.

Death certificates—the numerator—were all that the committee had to go by. But the reliability of these certificates varies greatly.

Unless there is an autopsy—and postmortems are held in only 20 to 30 per cent of all deaths—there is, if the cause of death is not obvious, no audit of the cause given in the certificate. Lung clots are often not obvious.

For women who had taken Enovid (which in this respect is believed to be no more or no less safe than other oral contraceptives), the committee's numerator again had to be what was available: the number of deaths reported to FDA and by the manufacturer, G. D. Searle & Co.

For its denominator, the committee used the number of women assumed to have been using Enovid during 1962. Precisely what that figure was, nobody—the company included—could possibly know.

This was dramatically illustrated last Oct. 16 in the *British Medical Journal* by Dr. Arnold Klopfer. "An inquiry to leading companies in this country and in the United States . . . produced estimates varying from five million to 20 million women all over the world taking these compounds daily," he said.

But if a mere 10 per cent fewer patients took Enovid than the Wright committee calculated, *Science* magazine has said, "the death rate . . . would come very close to statistical significance for all ages; and if 50 per cent fewer people took it, the rates would be very significantly greater."