ing Enovid be reported to us and to the Food and Drug Administration."[2] In the fall of 1965, a survey of the deaths so reported to the FDA indicated gross underreporting. Accordingly, in January 1966, arrangements were made for Dr. Schuyler Kohl, professor of obstetrics and gynecology at the Downstate Medical Center of the State University of New York, to visit all pharmaceutical firms marketing oral contraceptives and make a thorough investigation of the deaths reported and other pertinent facts.

Dr. Kohl's report, which is included in appendix 6 (p. 64) confirmed the earlier impression of the Committee in respect to underreporting of deaths. In fact, he found the magnitude of underreporting to be so great as to preclude drawing any conclusions from these data. The evidence was clear that the pharmaceutical firms concerned reported promptly any adverse reactions of which they were notified; the breakdown of this voluntary system of reporting was caused rather by the inadequate information about deaths on the part of physicians and other persons who were relied upon to report adverse reactions.

8. Taking into account the preponderance of young women among those using oral contraceptives, one would expect for each million users about 14 fatal cases of thromboembolic disease per year, including 10 deaths from pulmonary embolism and 4 deaths from cerebral embolism and thrombosis. Hence, the numbers of deaths expected in 1962 on the basis of the industry estimate of users (1,187,000) would be on the order of 12 and 5, respectively. It would seem prudent, however, to reduce these figures to, say, 10 and 4, respectively, to allow for a possible inflation of the estimated number of users.

According to the information obtained by Dr. Kohl, 20 deaths from all causes were reported to the manufacturers (and subsequently to the FDA) as having occurred among users of oral contraceptives in 1962. Of these, only 13 were due to "idiopathic pulmonary embolus"; that is, to an embolus without any demonstrable predisposing factor. This figure (*13*) is larger than the expected number of deaths from pulmonary embolism alone (*10*), but the difference is not statistically significant. This relationship of reported to expected deaths in 1962 is virtually the same as found by the Wright Committee which used the same or very similar basic data and a comparable procedure. (Report by the ad hoc Committee for the Evaluation of a Possible Etiologic Relation With Thromboembolic Conditions, submitted to the Commissioner of FDA, HEW).

9. It would appear, then, that the intense effort of 1962 produced about as many reports of fatal cases of pulmonary embolism among users of oral contraceptives as would be expected on the basis of the experience of the general female population of reproductive age. It will be noted, further, that the number of women taking oral contraceptives increased more than fourfold from 1962 to 1965. The survey estimate for the latter year (3,800,000 users) implies 38 expected deaths from pulmonary embolism. Acceptance of the industry estimate (5 million users) would raise this figure to 50 deaths.

Even without any causal relationship whatsoever it would be expected that the numbers of reported deaths among women taking oral contraceptives would augment proportionally with the increasing numbers of users. This, however, was not the case. The number of reported deaths due to unexplained pulmonary embolism in 1962 and 1965 were the same (*13*).

The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause they do so very infrequently relative to the number of users. The task force believes, nevertheless, that the only way in which this question can be answered definitively is through well-controlled epidemiological studies.

COPY OF LETTER FROM G. D. SEARLE & CO.

AUGUST 7, 1962.

IMPORTANT—DRUG CAUTION.

DEAR DOCTOR: We are addressing this letter to you in keeping with our policy of bringing to you all of the pertinent facts concerning our products and as a response to recent publicity dealing with the occurrence of thromboembolic phenomena coincident with women receiving Enovid.

Since its introduction there have been reported to us as of this date 28 cases of thromboembolic disease in the more than 1 million users of Enovid in the United States. Among these were 10 cases

[2] "Drug Caution" letter appended.