

the face of this spontaneous, rapid rise in the frequency of embolism, it becomes most difficult to find out whether there is any *additional* increase in embolism as a consequence of the use of the Pill.

One way to study the problem is to see whether the pill-takers show a higher frequency of such troubles than other groups. This was the approach taken by Drs. Drill and Calhoun when they compared the rate of thrombophlebitis in pill-takers with the rates in certain other populations. Their value of 0.55 cases per thousand women per year was no different from the rates of several other comparison not taking the Pill:

Incidence of thrombophlebitis in nonpregnant women of childbearing age

	Annual rate (per 1,000 women)
Based on:	
Hospital admissions (U.S. and Canada)-----	0.91
Visits to physicians (England)-----	1.3-2.6
Visits to physicians (U.S.A.)-----	1.2-3.0
Antenatal incidence-----	0.74
Combination contraceptive trials (50,781 w/y)-----	0.55±0.37
Monthly-check sequential trials (27,959 w/y)-----	0.56

These statistics were attacked on the ground that follow-up of the Pilltakers was not adequate and that cases of thrombophlebitis might have gone unreported. We therefore undertook a similar study in a collaborative trial we have been monitoring, where patients were questioned *every single month* as to their health. In an aggregate of over 360,000 months of experience in about 10,000 women, we came out with an answer of 0.56 cases per 1,000 women per year, in startling agreement with the figure of Drill and Calhoun. Evidently, even a much more careful followup and a low dropout rate failed to turn up significant numbers of unreported cases. However, we are the first to admit that such data are, *at best, only indicative that a substantial risk does not exist*. They do not constitute proof or disproof of the original question.

The best way known to obtain answers to such difficult problems is to carry out what is called a prospective study. Such a study, for example, would observe 20,000 women started on the Pill and 20,000 women started on some other type of contraception for 5-10 years, and see if there is eventually a difference in the frequency of clots. This is obviously a monumental and costly undertaking. A quicker and cheaper way to try and arrive at an answer is to take a backward look instead of a forward look. This is called a retrospective study. It hinges on the matching of patients with thrombosis with other people ("controls") who are very similar in age, medical history, habits, etc., but who have not had thrombosis, and then to see whether or not there are equivalent numbers of Pill-takers in both groups. The crucial problem with such studies is the word "matching". Since we do not know all the factors which are at work in the thrombosis problem, it is impossible to match correctly for everything that might affect the comparison. Therein lies the great weakness of such studies. The widely quoted British study of Vessey and Doll falls apart on this very ground. After they had completed their efforts at matching, it turned out that the thrombosis group had a considerably different history with regard to previous thrombosis than the control group. To many statisticians this invalidates the study right there, since after-the-fact adjustments are not permissible. But even if this were acceptable, it now turns out that English women who take the Pill are, among other things, heavier smokers than women who do not take the Pill. Smoking itself has a definite effect on the frequency of thrombosis. Now the question arises, whether the differences attributed to the Pill in this study are not perhaps due to differences in the smoking habits of the two sets of subjects. Thus, at the very least, the conclusions of the British statisticians are open to question. There are many other technical reasons why this and the other British studies are held in doubt by many scientists; I had the privilege of being invited to discuss this question before a national assembly of biologists just last April. This is not the time or place to bore you with the technical details; the critical analysis of the British studies will appear in the scientific literature very shortly.

Almost at the same time that the British retrospective study was going on, a similar but considerably better-designed effort was underway in the United States. The American study avoided some of the pitfalls of the British study in