The New England Journal of Medicine

Owned and Published by the
Massachusetts Medical Society

PROSPECTIVE authors should consult "Information for Authors," which appears in the first issue of every volume and may be obtained from the *Journal* office.

ARTICLES with original material are accepted for consideration with the understanding that, except for abstracts, no part of the data has been published, or will be submitted for publication elsewhere, before appearing here.

NOTICES should be sent at least 30 days before publication date.

ALTHOUGH all advertising material accepted is expected to conform to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

REPRINTS: Reprints are available in minimum quantities of 50. To order, please contact the Business Office at the address provided below.

SUBSCRIPTION PRICES: USA: $60 per year (interns, residents $35 per year; students $30 per year). Outside USA (U.S. funds only): $75 per year (interns, residents $55 per year; students $45 per year). Remit payments and correspondence to NEJM Subscriber Service Dept., 1440 Main St., Waltham, MA 02254-0803. Please include current mailing label with renewal order.

EDITORIAL OFFICES: 10 Shattuck St., Boston, MA 02115.

BUSINESS AND SUBSCRIPTION OFFICES: 1440 Main St., Waltham, MA 02254.

ORAL CONTRACEPTIVES — TIME TO TAKE STOCK

ABOUT 1 in 13 women in the United States can expect to have breast cancer, and there is abundant evidence to suggest a hormonal component in its causation.[1] Not surprisingly, therefore, the widespread use of oral contraceptives has been a source of continuing concern since they were introduced in the early 1960s — a concern heightened by our knowledge that hormonally related factors, such as age at first pregnancy, can continue to influence the risk of breast cancer for an entire lifetime. In this issue of the *Journal*, the findings of the Cancer and Steroid Hormone Study provide welcome reassurance.[2] In a well-designed case–control study — the largest to date, involving almost 5000 cases and 5000 controls — it was possible to assess many of the questions raised in earlier, less extensive, investigations. The present evidence is against an increased risk of breast cancer in those who use oral contraceptives or who have used them and discontinued them for up to 15 years.

The evidence is also against an increased risk for many subgroups of users about whom concern has been expressed in the past (e.g., women with benign breast disease).[1] It has recently been suggested that prolonged use of oral contraceptives before the age of 25 years[3] or by nulliparous women[4] may confer an increased risk; certain types of oral-contraceptive formulations thought to be of high progestational potency have also been thought to increase the risk.[3] Fortunately, there were sufficient data in the Cancer and Steroid Hormone Study to permit statistically stable estimates of breast-cancer risk within these subgroups.[2,5] Again, the evidence was against an increased risk.

Any study gains in credibility when other well-designed investigations based on different research strategies yield similar results. Thus, it is encouraging that the present findings (based on a case–control study with population-based controls) accord with those of other large case–control studies that have been hospital-based[6] and with those of follow-up studies.[7]

A reasonable conclusion is that the oral contraceptives used in the United States do not increase the risk of breast cancer. But there are some important qualifications: First, latency intervals longer than 15 years following the discontinuation of oral contraceptives remain to be evaluated. This is of particular importance because the incidence of breast cancer climbs steeply after the age of about 40.[1] Second, it may be that we still lack adequate information about certain subgroups, such as women who begin to use oral contraceptives soon after the menarche, when the breasts are growing rapidly. Third, oral-contraceptive formulations have changed over time, and different formulations are used in different countries; what has been true for patterns of oral-contraceptive use until now may not be true for the future, and what is true for the United

States may not be true for other countries. Surveillance of the risk of breast cancer should continue for the entire lifetimes of users and in many parts of the world.

So far, the reassuring findings about the risk of breast cancer weigh heavily in favor of the safety of oral contraceptives. What matters ultimately, however, is the total risk of mortality and serious morbidity from all causes as compared with the benefits. On the risk side of the equation there are, to be sure, serious complications of oral-contraceptive use, foremost among them being vascular thrombosis (venous thromboembolism, stroke, and myocardial infarction).[8] Among healthy women of childbearing age, however, thrombosis is so uncommon that the excess incidence due to oral-contraceptive use is probably very low in absolute terms (except, perhaps, for the occurrence of myocardial infarction in users over the age of 35 or 40 if they also smoke).[8] Other established complications of oral-contraceptive use include liver tumors,[9] but they are so rare that the increased risk, although real, poses negligible public health problems.

There are also physiologic and metabolic effects of oral-contraceptive use, such as elevation of blood pressure, hyperglycemia, and changes in lipoprotein patterns that may tend to accelerate atherogenesis.[8] In support of this possibility, there is evidence that long-term use may, after discontinuation, continue to increase the risk of myocardial infarction.[8] If this is confirmed, it will be important to determine whether the elevated risk persists beyond the age of 50, when myocardial infarction becomes common.

On the benefit side of the equation, oral contraceptives enable women to avoid unwanted pregnancies and their associated morbidity and mortality more effectively and conveniently than any other reversible method of contraception. Moreover, they can do so without impeding the ability of women to bear children subsequently at times of their choosing.[10] There are also some beneficial side effects: Oral contraceptives (with the possible exception of sequential preparations) actually appear to reduce the risks of cancer of the uterus and ovary.[9]

This brief list of the risks and benefits is by no means complete, but the picture is clear: Oral contraceptives have given women unprecedented control over their reproductive function, but at a cost. From a public health viewpoint, as best we can judge on the present evidence, that cost is acceptable, at least in the United States — although it should be remembered that the risk of breast cancer after very long latency intervals remains to be assessed and cannot be assessed for at least another decade. In addition, the cardiovascular effects of long-term use remain to be clarified.

Finally, the favorable statistical odds are no comfort to those women unfortunate enough to have experienced one or another of the complications of oral-contraceptive use. We should recognize, however, that our thinking can be subject to a subtle bias: We tend selectively to notice and remember the victims and not the beneficiaries. If we overcome that bias, we can recommend oral contraceptives with the reassurance that the vast majority of users will experience only the benefits. If we wish to reduce the risks further, we are obliged to continue the search for even safer contraceptives.

Drug Epidemiology Unit
Boston University School of Medicine
and School of Public Health
Brookline, MA 02146

SAMUEL SHAPIRO,
M.B., F.R.C.P.(E.)

REFERENCES

1. Kelsey JL. A review of the epidemiology of human breast cancer. Epidemiol Rev 1979; 1:74-109.
2. The Cancer and Steroid Hormone Study Group. Oral-contraceptive use and the risk of breast cancer: the Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. N Engl J Med 1986; 315:405-11.
3. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 1983; 2:926-30.
4. McPherson K, Neil A, Vessey MP, Doll R. Oral contraceptives and breast cancer. Lancet 1983; 2:1414-5.
5. Stadel BV, Rubin GL, Webster LA, Schlesselman JJ, Wingo PA. Oral contraceptives and breast cancer in young women. Lancet 1985; 2:970-3.
6. Rosenberg L, Miller DR, Kaufman DW, et al. Breast cancer and oral contraceptive use. Am J Epidemiol 1984; 119:167-76.
7. Vessey MP, Doll R, Jones K, McPherson K, Yeates D. An epidemiological study of oral contraceptives and breast cancer. Br Med J 1979; 1:1757-8.
8. Stadel BV. Oral contraceptives and cardiovascular disease. N Engl J Med 1981; 305:612-8, 672-7.
9. Stubblefield PG, Oral contraceptives and neoplasia. J Reprod Med 1984; 29:Suppl 7:524-9.
10. Vessey MP, Wright NH, McPherson K, Wiggins P. Fertility after stopping different methods of contraception. Br Med J 1978; 1:265-7.

NON-Q-WAVE MYOCARDIAL INFARCTION

THIS issue of the *Journal* contains two important papers on non-Q-wave myocardial infarction.[1,2] The rapid evolution of therapy for Q-wave myocardial infarction with the increasing use of thrombolytic procedures and early coronary angioplasty makes this a good time to reevaluate the pathophysiologic aspects of non-Q-wave infarction and the treatment of this condition.

In recent years, there has been abundant editorial comment about nontransmural and transmural myocardial infarctions and the relation between the pathological findings in these conditions and the presence of abnormal Q waves on the surface electrocardiogram.[3,4] Although some disagreement may still exist, I believe that several points are now established. First, it is clear that an abnormal Q wave on the electrocardiogram is not a sensitive predictor of the presence or absence of transmural myocardial necrosis, as demonstrated by pathological examination. For this reason, the terms, "Q-wave infarction" and "non-Q-wave infarction" are preferable to "transmural infarction" and "nontransmural infarction" when one is classifying a patient with myocardial infarction. Second, patients with initial non-Q-wave infarctions have a lower hospital mortality rate but a higher rate of reinfarction