The New England Journal of Medicine

 owned and published by the Massachusetts Medical Society

 Barry M. Manuel, M.D. President
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 EXECUTIVE OFFICES

 New England Journal of Medicine, 10 Shattuck St., Boston, MA 02115-6094.
 Telephone: (617) 734-8888, FAX: (617) 734-4882
 Business subscription office: 140 Main St., Waltham, MA 02154-8649.

 EDITORIALS

 THE INTERPRETATION OF EPIDEMIOLOGIC STUDIES

 The Journal is receiving a growing number of epidemiologic reports of associations between diseases and possible risk factors. The risk factor in question is often a habit or type of behavior, some element of diet or lifestyle that can presumably be changed. The reports are therefore often of great interest to the popular media and the public, as well as to physicians interested in preventive medicine.

 Why are we seeing so many of these kinds of studies now? One reason is that the major diseases now affecting Americans are chronic, degenerative diseases that probably have several contributing causes, some of which have to do with lifestyle, operating over long periods. Each contributing cause may have only a small role. For example, obesity is well established as a risk factor for coronary heart disease, but it is only one of several, none of which can account for the total incidence of this disease.

 It is usually very difficult to investigate such risk factors through experimental (or interventional) studies. In some cases it is impractical and in some it is unethical. For example, researchers cannot expose half of a group of children to lead for 10 years to compare their IQs 20 years later with those of the unexposed children. We must therefore rely on epidemiologic (or observational) studies. These are of two principal types: case-control studies and cohort studies. Case-control studies begin with patients who already have the disease in question (case patients) and compare the frequency of past exposure to the risk factor in question with the frequency of exposure in a group without the disease (controls). Cohort studies start before anyone has the disease; they follow people known to be exposed to the possible risk factor and compare the frequency with which the disease in question develops with its frequency in a group not exposed to the risk factor. Either type may demonstrate that a disease or other outcome is more likely in those with a particular exposure. Although such studies usually cannot prove that the exposure is the

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cause of the disease, they may offer strong support for that hypothesis.

Epidemiologic studies of both types are subject to many biases and therefore present formidable problems in design and execution and even greater problems in interpretation. The chief difficulty is that it is nearly impossible to find groups of people who are alike in every way except for the exposure or disease in question. Usually a number of types of behavior or exposures tend to occur in combination with one another. For example, cigarette smokers are more likely to drink alcohol than are nonsmokers. So when an epidemiologic study shows a link between cigarette smoking and a disease, it is necessary to determine whether the real association is with smoking, drinking (termed a confounding variable in this case), or the combination.

Although there are statistical methods for neutralizing confounding variables, they are not perfect, and they are of no use whatsoever unless the confounding variables are known and measured. For example, epidemiologic studies have shown an association between premature births and lack of prenatal care, but it could be that women who can afford prenatal care are more likely to carry babies to term because such women are, say, better nourished. Similarly, one can imagine other, unknown confounding variables in this association, or ones, such as education, that are difficult to characterize. Furthermore, if a confounding variable is very important as compared with the risk factor being studied, attempts to control for it may easily be inadequate. If, for example, some aspect of socioeconomic status is a major confounding variable in a study of a weak association, it may be necessary to characterize socioeconomic status very precisely, and even then attempts to factor out its influence may not succeed.

Considerations of this kind are well illustrated by the interesting study of Rubin, reported in this issue of the Journal, showing a weak association between passive smoking and measures of ill health in children with cystic fibrosis. Although a direct connection is certainly plausible, it is also possible that socioeconomic factors, which were not controlled for in this study, influenced both how well the parents cared for their children and whether they decided to smoke. As Rytander points out in his letter to the editor in this issue, studies of passive smoking are extremely difficult to design and interpret.

How, then, should we evaluate epidemiologic studies? And, in particular, how do the editors of the Journal decide which ones warrant publication?

When an epidemiologic study shows that an exposure is associated with an outcome, an important question for us is the size of the effect. Does the exposure increase the risk manyfold, twofold, or perhaps by only 20 percent (a relative risk of 1.2)? An important reason for being concerned about the size of the effect is that unknown or inadequately accounted for confounding variables can easily produce artificial small effects (or mask real ones). It is far less likely that the confounding variables account for large effects.

The question of the size of the effect is very different from that of the statistical significance of the association (usually expressed as a P value or confidence interval). The P value is a measure of the probability that the finding is due to chance, and it reflects the size of the sample studied. If a study is large enough, even a very small effect may have a low P value and therefore be statistically significant (or a large effect, in a small study, may not be). This is true even if the association is entirely spurious because of a confounding variable or a systematic bias in the collection of data. In either case a statistically significant result could be obtained artificially. This fact is underscored by the frequency with which studies reporting small but statistically significant effects are contradicted by other studies—a subject discussed by Bailar.

In addition to being concerned about the size of the effect found in an epidemiologic study, the editors are also concerned about whether the association between the exposure and the outcome is biologically plausible. Does it conform with everything we know, or are the results inexplicable or inconsistent with other data? The Journal would be unlikely to publish a report of an epidemiologic study if it purported to find an effect that was both weak and implausible, although we might be willing to publish a report of a small effect that made biologic sense or a large effect that did not.

When an epidemiologic study describing a new risk factor passes critical peer review and is published, how should clinicians respond to it? First, they should probably not advise their patients to change their lifestyles on the basis of one study, no matter how well executed, unless the risk is large, the finding makes sense, and the change in lifestyle would not be onerous. In general, clinicians should wait until the association is confirmed by other studies, because the opportunities for bias are so many that one study is rarely conclusive.

Even after a risk factor is fairly well established—say, a high serum cholesterol level as a risk factor for cardiovascular disease—clinicians should ask themselves what this association means for their individual patients. If the risk is very small, a person may reasonably not wish to change his or her lifestyle, as pointed out by Brett. For example, the 10-year risk of death from cardiovascular disease is 4.9 percent in middle-aged men with cholesterol levels over 6.2 mmol per liter (240 mg per deciliter), as compared with 1.7 percent in those with cholesterol levels under 5.2 mmol per liter (200 mg per deciliter). This difference in risk of about 3 percent (which may become greater after 10 years) may not be enough to induce an otherwise healthy man to try to lower his cholesterol level. Even risk factors with very large effects may not be important to individual patients if the disease in question is rare.

Despite the limitations of epidemiologic studies for use in advising individual patients, this type of re-
search can have great public health implications. Risk factors that are unimportant for individuals may be important when the effect is multiplied over the population as a whole, especially if the disease is common. For example, the Lipid Research Clinics trial showed that using cholestryamine to lower serum cholesterol about 9 percent in middle-aged men with high cholesterol levels reduced their seven-year risk of coronary events from 8.6 to 7 percent. Although such a reduction may not seem worthwhile to an individual, when spread over the estimated 1 to 2 million Americans with similar cholesterol levels, it could account for up to 32,000 fewer coronary events over the first seven years. Furthermore, discovering associations between exposures and disease, even when the effect is small, may be important in elucidating the pathogenesis of the disease. Certainly, defining the epidemiology of the acquired immunodeficiency syndrome was crucial in leading researchers to the cause.

There is no question that epidemiologic studies of risk factors are of growing interest and importance, both for individuals and for the public health. It is important, however, to remember the pitfalls in interpreting them and to be cautious in advising patients on the basis of single or conflicting studies. This is particularly true of studies that purport to show only weak associations between exposures and disease. These should be evaluated more critically by researchers and clinicians alike.

MARCIA ANGELL, M.D.

REFERENCES


COMING OF AGE — THE CHEMOPREVENTION OF CANCER

With the aging of the population and the continued fall in rates of mortality from cardiovascular diseases, cancer will emerge soon after the year 2000 with the dubious distinction of being the leading cause of death in the United States. Unfortunately, dramatic therapeutic successes in the treatment of cancer plateaued in the mid-1970s, and advances since have been incremental. Whether the remarkable progress in our understanding of the biologic and genetic underpinnings of normal and transformed cellular growth in the past 15 years will be translated into substantial therapeutic benefit remains to be demonstrated. Alternatives to therapy of late disease need to be developed for the control of cancer, chemoprevention, or the chemical prevention of cancer formation, is one such novel approach.

The process of cancer formation, or carcinogenesis, has been more and more precisely defined with the availability of increasingly sophisticated molecular and biochemical tools. Increased understanding of the genetic milieu that predisposes certain persons to cancer will offer an opportunity to define the risk of cancer in individuals and to modulate that risk with the use of inhibitors of biochemical alterations in incipient cancer cells. The expression of tumor transformation in vitro and in vivo can be inhibited by a variety of compounds. Normal dietary constituents and pharmacologic agents may be candidates for chemopreventive activity; their prototypes are beta carotene and synthetic retinoids, such as isoretinoin (13-cis-retinoic acid), respectively. In the early 1980s, clinical studies with small numbers of patients established that synthetic retinoids could inhibit the progression of many neoplastic conditions and some neoplastic states (reviewed in Lippman et al.1). Dietary epidemiologic studies provided substantial support for the notion that certain vitamins, micronutrients, and other components of food enhanced or inhibited the development of cancer in humans.2,3 Prominent among the dietary constituents implicated as preventive agents for cancers of the lung and other organs was beta carotene, a substance that has frequently been suggested for human use because of its easy availability and low toxicity, even in very high doses.3

In this issue of the Journal, the results of two large randomized clinical trials of chemoprevention are presented.1,2 They have been carefully designed and impeccably conducted, but they have led to different conclusions. Beta carotene did not lower the rate of development of new basal-cell or squamous-cell cancers of the skin in subjects with previous skin cancers. In contrast, isoretinoin did lower the rate of development of second regional tumors in patients with a previous oral cancer.

Why these opposite results? The most obvious explanation is that beta carotene and isoretinoin represent two quite different inhibitors of carcinogenesis. In most model systems beta carotene is a weak anticarcinogen, whereas isoretinoin is a potent inhibitor of cancer formation. However, since beta carotene has recently been demonstrated to reverse a preneoplastic condition in humans — a step rather late in the pathway to cancer — other explanations should be sought.4

In the beta carotene study, the authors thoroughly address possible reasons for the negative results, but they do not consider an important alternative possibility: that the high levels of beta carotene may have