viously been obtained on a frequent basis) are no longer required. Also, follow-up chest x-rays (which previously had been required seven times in the first follow-up year) are now required at yearly intervals only. These alterations in follow-up testing procedures should enable health care resources to be used more productively without affecting the quality or the quantity of life of patients with newly diagnosed melanomas. Similar information regarding the follow-up of other common cancers (eg, prostate and lung) should also provide valuable information.

Given the lack of a clearly defined consensus regarding the follow-up of most cancer patients after primary therapy, what actually occurs in practice? Generally, curatively treated patients have been followed according to patterns that are based on historical practices—practices that were often started decades ago when substantially less was understood about the natural history of malignant diseases. Community standards of care seem to have often evolved according to dominant individual perceptions. Any practicing clinical oncologist can attest to the large variation in follow-up testing procedures. There has been little incentive to evaluate follow-up practices.

Nonetheless, with all the scrutiny of health care resources and their rational utilization, it is mandatory that we as physicians explore the use of guidelines as part of an organized strategy for follow-up of curatively treated cancer survivors. In diseases such as breast cancer, in which there are extensive applicable data including large randomized clinical trials,[2-4] the development of guidelines using pertinent methods[6] should be relatively straightforward. The development of guidelines for follow-up of colorectal cancer survivors is not as easy, since there are no available data from large randomized trials addressing different follow-up strategies and, as yet, there are no good published reports looking at the utility of follow-up testing on recently completed large prospective trials. Nonetheless, the development of practice guidelines by groups of individuals working together (eg, in a large group practice) should help to provide better uniformity and better patient care. An initial step toward such guideline development is to survey local physician experts about follow-up recommendations for standard cases (eg, node-negative colorectal cancer). Collating this information, discussing it, and reviewing the available medical information can lead to the development of initial guidelines; these guidelines may contain options when the available scientific information does not provide definitive answers.

It is vital to realize that evidence-based guidelines provide direction, as opposed to being restrictive. Deviations from guidelines for individual patients are to be expected. However, appropriate practice guidelines should be helpful in providing information regarding current best practice and in dissuading physicians from ordering inappropriate tests. Also, appropriate guidelines should serve as guideposts that could be used to help decide whether expensive new agents or tests (eg, new radioisotope-tagged monoclonal antibodies) should be incorporated into standard clinical practice.

Given the lack of ideal data and the reservations mentioned herein, let me step out on a limb regarding recommendations for following colorectal cancer survivors by suggesting that frequent blood and imaging tests will not be productive in the first follow-up year. This is because most cancer recurrences during this period are not likely to be resectable for cure. Surgically resectable recurrences are most likely to be detected during the second through fourth follow-up years. Judicious use of blood tests and chest x-rays during this time will signal a few resectable metastases. Although clearly not accepted as routine clinical practice, ultrasound imaging of the liver during the second through fourth follow-up years is an appropriate research question in the search for a sensitive and cost-conscious test.

In conclusion, the way in which we follow cancer survivors has been relatively neglected in the past. This subject deserves appropriate attention using available scientific methods. The development of evidence-based guidelines regarding the follow-up of cancer survivors should better serve the needs of our patients and society in general.

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Which Comes First in Non–Insulin-Dependent Diabetes Mellitus: Insulin Resistance or Beta-Cell Failure? Both Come First

The curious physician trying to understand the pathogenesis of non–insulin-dependent diabetes mellitus (NIDDM) has every reason to be mystified by the barrage of conflicting claims about the primacy of beta-cell failure and insulin resistance.

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How can the argument go on for so long without a clear answer? Probably because we keep trying to view NIDDM as being simpler than it really is, and because we expect that the first identifiable lesion will lead us to the primary cause. Since there is general agreement that a combination of both environmental and genetic forces leads to NIDDM, it is probably counterproductive to think in terms of a primary cause or something that comes first. The major environmental prob-

lem seems to be our modern obesity-promoting lifestyle of limited physical activity and abundant food. Not only is obesity associated with insulin resistance, but sedentary behavior by itself leads to reduced insulin action on muscle. In addition, there are strong genetic determinants for obesity, for insulin resistance that is unrelated to obesity, and presumably for beta-cell dysfunction that somehow work together to culminate in NIDDM. It is now clear that the development of NIDDM is almost always associated with insulin resistance and always with a failure of beta cells to maintain normal glucose levels.

See also p 1855.

Why are we obsessed with finding the first phenotypic abnormality for a disease caused by environmental and genetic factors? From a health point of view, this makes sense; early identification of those at risk for NIDDM can lead to earlier therapeutic intervention. However, the hope that identification of an early phenotypic change will clarify the causes of NIDDM is more problematic because it is based on the questionable premise that such a finding would likely lead to the underlying genetic abnormality. Part of the problem is that NIDDM results from a balance of varying determinants that are difficult or impossible to measure and therefore cannot be appreciated as individuals progress from a normal to a diabetic state. For example, there may be critical genetic determinants for maintaining beta-cell mass over a lifetime that could never be found with early phenotypic testing. There may also be genetic differences in the propensity for islet amyloid formation that will only cause problems in midlife and when combined with other pathogenic factors such as mild hyperglycemia. Similarly, specific lesions of the insulin-signaling pathways in muscle and liver may not be apparent until they are brought out by age and environmental factors.

The balance between these environmental factors and genes appears to vary among different racial and ethnic groups. Comprehensive studies of Pima Indians document the major contributions of lifestyle, obesity, and insulin resistance to the development of NIDDM[1]; observations on other ethnic groups such as Mexican Americans arrive at similar conclusions.[2,3] The balance of interactions appears to be different in white populations of European origin, as suggested by the study by Pimenta and colleagues in this issue of *JAMA*, which provides evidence for a visible early contribution of beta-cell failure.[4] But this study does not prove that beta-cell dysfunction is the dominant determinant for progression to NIDDM in whites. Although not emphasized in the article, the subjects with a first-degree NIDDM relative were certainly relatively insulin resistant; they had a median body mass index of 26.4 kg/m^2, a level known to be associated with an increased risk of NIDDM. In the Nurses' Health Study, even women with an index of only 22.0 to 22.9 kg/m^2 had a threefold age-adjusted relative risk compared with women with an index less than 22 kg/m^2; those with an index of 25.0 to 26.9 kg/m^2 had an eightfold risk.[5] Also, it must be pointed out that the control group was not representative of the general white population because they were weight matched to the first-degree relatives. With a body mass index of 26.9 kg/m^2, the control group was also overweight and at increased risk for developing NIDDM compared with a thin, physically active population. Thus, the results of the present study are in agreement with general thinking about NIDDM. In this white population, the cooperative interactions between environment, insulin resistance, and insulin secretion probably lead to diabetes in much the same manner as occurs in other populations; the similarities are more apparent than the differences. Nonetheless, the study does provide valuable insight into the variable pattern of diabetes development in different populations.

New methodologies and insights will no doubt foster continuation of the search for the earliest phenotypic abnormalities in NIDDM. There will be good reasons to do so, but expectations that the next earliest lesion to be discovered will be the key to the cause of NIDDM should be lowered. Attention is now rapidly shifting to the more promising approach of genetic analysis, but easy answers may not emerge soon. Many candidate genes have already been analyzed with negative findings. More sophisticated gene-screening approaches will be required and are already being carried out on a variety of population groups.[6] It will not be surprising to find that complicated gene combinations are involved and that new genes coded for unknown proteins will be important. Eventually it should be possible to predict how a particular genetic profile can interact with the environment to cause NIDDM, and this should greatly facilitate the identification of those at risk. Furthermore, the discovery of the genetic basis of NIDDM should promote the development of new pharmaceutical approaches. Over the past few decades, debate and argument over whether insulin resistance or defective insulin secretion is the earliest lesion have provided valuable stimulation to research on the pathogenesis of NIDDM. But now the limitations of what can be learned from the next earliest phenotypic lesion should be appreciated; the real cause of NIDDM can be found in the genome at conception. Now we can look forward to a shift in the debate from "what comes first?" to "which genes are most important?"

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