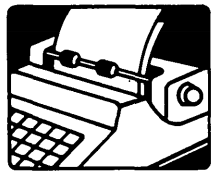
Editorial



Evidence, Implications, and Corollaries

An issue of fundamental importance to patients with diabetes mellitus and health professionals who care for them is the relationship of diabetic complications to the deranged metabolism (hyperglycemia, insulinopenia, and associated metabolic alterations). There is substantial *evidence* that at least the microvascular complications (retinopathy, nephropathy), and perhaps neuropathy, develop as a consequence of, or are in part influenced by, the metabolic dysfunction. This evidence has been reviewed previously in this journal and elsewhere.[1-4] An *implication* is that the degree of metabolic control achieved by therapy might be expected to influence the development of these complications, and that normalization of metabolic aberrations might prevent, delay, or substantially reduce the severity of these complications. The clinical *corollary* of such implications is that we should expend our best efforts in devising and implementing therapeutic strategies that most closely approximate metabolic normality.

Controversy and debate on the above issues has been extant. It has focused on all three levels—the evidence, the implications, and the corollary. In my view the evidence supporting the relationship between complications and metabolic dysfunction is overwhelming. As with most, if not all, scientific tenets, however, that conclusion must be tempered with the recognition that it is tentative, interpretative, and not proven. Scientific experimentation involves hypothesis testing, with the finite possibility of error always present. The dictionary includes "tentative" within the definition of experimentation, and scientists universally accept that newer experimentation often makes old conclusions obsolete. The accumulation of data, particularly over the last decade, is such that today the evidence itself engenders little debate, although until very recently the evidence has been a focal point of the controversy.

The implications are derived not only directly from the evidence, but from additional reports of clinical experience. There are many such reports, reviewed elsewhere.[1-4] Some, notably the Brussels study,[5] involve prospective, longitudinal observations of large numbers of patients. Concerning the Brussels study, I have previously noted in these columns[6] that the absence of random allocation of subjects to various groups, in terms of degree of diabetic control sought, leaves unanswerable the question of whether patients who achieved "good" control and escaped complications are in some way different from those who achieved only "poor" control and suffered complications. Only a randomized design can negate that criticism. Those who would challenge the implications stated above invariably demand that a randomized, prospective clinical trial be conducted. The University Group Diabetes Program study[7] was designed as such a trial, in the hope of answering this question for a defined subset of the diabetic population. Unfortunately, that study became embroiled in other controversies which we will not discuss here. Recently, the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK), after several years of planning and discussion, announced a multicenter collaborative clinical trial, using a randomized prospective design, "to determine whether strict control of blood glucose concentration is effective in preventing or ameliorating the vascular complications of insulin-dependent diabetes mellitus."[8] This study would directly test one of the implications in at least one type of diabetic patient.

The corollary raises other issues. How do we define "metabolic normality"? How closely should it be approximated? How do we measure it? What are the downside costs and risks of attempting to closely approximate metabolic normality? In fact, it indeed may be hard to achieve excellent metabolic control, in terms of time, effort, and direct costs expended by patients and professionals. The use of patient self-monitoring of blood glucose[9-11] and insulin infusion systems[12,13] have facilitated the attainment of improved glycemic control.

There has been considerable debate and controversy concerning the evidence about the relationship of diabetic complications to the metabolic derangements. I suspect that the intensity and ferocity of the debate was largely based on the fact that the implications and corollary were such that implementation was extremely difficult with "conven-

tional" treatment strategies. Rather than admit that, the debate was displaced to center on the evidence itself and the details of the scientific experimentation. This provided relief to doctors: "If the benefits of achieving the best control feasible are unproven, then I need not feel compelled to expend the considerable extra effort necessary to attain that degree of control." Recently, the level of debate has all but subsided. Admittedly, the weight of the scientific evidence has increased the last several years. I suspect, however, that the lessening of the frequency and intensity of debate about the evidence over the last few years is partly for another reason. Namely, it is now recognized that we are able to deal more directly with the corollary: albeit with effort, substantially improved control is attainable in many patients.

In my view, answering the questions posed by the corollary is a valuable and productive endeavor. Past therapeutic strategies often have ignored basic physiology, the pathophysiology of diabetes, and/or the pharmacokinetics of insulin availability. Patient self-monitoring of blood glucose has permitted the definition of targets for glycemic control and the measurement of control achieved in ordinary life. Insulin infusion systems have resulted in the development of more physiologic treatment strategies and a renewed interest in insulin pharmacokinetics, facilitating the design of insulin regimens aimed at improved glycemic control.[14–17] Attention has turned away from debate and controversy over whether control should be attained to discussion of how best to achieve glycemic control.

This change in emphasis has pedagogic advantages as well. Too often in the past practicing physicians would listen to the experts debate the evidence or its implications. They would leave the room confused, convinced the diabetes community did not know how to treat diabetes, and with no reason to alter their clinical behavior. Certainly, there was no clear message. The entertaining debates were educationally useless, in terms of clinical behavior.

Although the evidence is overwhelming, there is still a degree of lingering uncertainty, which might be resolved by a more perfect experiment. The NIADDK collaborative study has been heralded by many as that experiment, and it is reasonable to pose questions about the conduct and design of that study. Indeed, as this editorial is being written, the participants in that study are being selected. By the time this editorial is read, those participants will be initiating a series of meetings to develop their detailed protocols. They face a real challenge. Is it possible to design a protocol that includes *random* allocation of therapies to a *representative* sample of patients with insulin-dependent diabetes mellitus, that is both *reasonable* and *realistic*?

The request for applications (RFA) asks for protocols that will compare excellent glycemic control with "conventional" treatment. Although not explicitly stated, an assumption is that excellent control will be attained by continuous subcutaneous insulin infusion (CSII). Question: is patient self-monitoring of blood glucose (SMBG) a component of "conventional" treatment? If yes, will there be a clinically meaningful difference between treatment groups? The use of SMBG very likely would dampen such differences. Moreover, only patients willing to embark on SMBG would sign the informed consent, thus precluding a segment of IDDM patients and resulting in a nonrepresentative sample. If no, educated patients who have learned of SMBG might be expected to decline consent that would have a 50% chance of assigning them to a "conventional" treatment group. The exclusion of these patients, who might otherwise be expected to be the best adherents to any protocol, would also result in a nonrepresentative sample. In either circumstance, it is possible to propose that, via a "second consent" process, those subjects who decline consent be followed with assessments of control and development of complications. This would prevent the exclusion of subjects who decline the main protocol and would permit their longitudinal evaluation. However, the treatment these patients receive would not be randomly allocated (although it might be more akin to "conventional" practice in the community). Thus, although random allocation of treatments to enrolled subjects can be assured via telephone assignment of treatment from a coordinating center, those subjects enrolled cannot be expected to be representative of all IDDM subjects.

An issue that requires contemplation concerns which is the better design: (1) random allocation of treatment to a nonrepresentative sample (the proposed NIADDK collaborative study), or (2) nonrandom allocation of treatment to a representative sample (the Brussels study). The Brussels study is completed. The NIADDK study is in the planning phase. Given the very large commitment of limited fiscal resources to the NIADDK study, and given the difficulties encountered in the UGDP study, the NIADDK investigators will be closely scrutinized. It is incumbent upon them to weigh carefully all details of study design and execution. In addition, as noted earlier, to be applicable to the diabetic populations at large, the protocol must be reasonable and realistic. Is it possible to achieve all four: random, representative, reasonable, and realistic?

Meanwhile, other investigators will continue to strive to define and refine our methods of treating IDDM. Newer advances and developments will improve our ability to attain optimal control. In the interim, pending these developments and the results of the NIADDK study, it seems to me that it is incumbent upon clinicians to strive for the best control achievable in any given patient.

JSS

REFERENCES

[1] Skyler, J. S.: Complications of diabetes mellitus: relationship to metabolic dysfunction. Diabetes Care *2*: 499–509, 1979.

[2] Tchobroutsky, G.: Relation of diabetes control to development of microvascular complications. Diabetologia *15*: 143–52, 1978.

[3] Davidson, M. B.: The case for control in diabetes mellitus. West. J. Med. *129*: 193–200, 1978.

[4] Brownlee, M., and Cahill, G. F.: Diabetic control and vascular complications. Atherosclerosis Rev. *4*: 29–70, 1979.

[5] Pirart, J.: Diabetes mellitus and its degenerative complications:

a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care *1*: 168–88, 252–63, 1978.

[6] Skyler, J. S.: Editorial. "Control" and diabetic complications. Diabetes Care *1*: 204–205, 1978.

[7] University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I. Design, methods, and baseline characteristics. Diabetes *19*(Suppl. 2): 747–88, 1970; II. Mortality results. Diabetes *19*(Suppl. 2): 789–830, 1970; III. Clinical implications of UGDP results. JAMA *218*: 1400–10, 1971; IV. A preliminary report on Phenformin results. JAMA *217*: 777–84, 1971; V. Evaluation of Phenformin therapy. Diabetes *24*(Suppl. 1): 65–184, 1975; VI. Supplementary report on nonfatal events in patients treated with tolbutamide. Diabetes *25*: 1129–53, 1976; VII. Mortality and selected nonfatal events with insulin treatment. JAMA *240*: 37–42, 1975.

[8] National Institute of Arthritis, Metabolism and Digestive Diseases: Request for research cooperative agreement applications: clinical centers for a collaborative clinical trial on the relationship between blood glucose control and vascular complications of insulin-dependent diabetes mellitus. RFA NIAMDD 81-01.

[9] Tattersall, R. B.: Home blood glucose monitoring. Diabetologia *16*: 71–74, 1979.

[10] Symposiumon home blood glucose monitoring. Diabetes Care *3*: 57–186, 1980.

[11] Symposium on blood glucose self-monitoring. Diabetes Care *4*: 392–426, 1981.

[12] Symposium on insulin delivery devices. Diabetes Care *3*: 253–370, 1980.

[13] Soeldner, J. S.: Treatment of diabetes mellitus by devices. Am. J. Med. *70*: 183–94, 1981.

[14] Phillips, M., Simpson, R. W., Holman, R. R., and Turner, R. C.: A simple and rational twice daily insulin regime. Q. J. Med. *48*: 493–506, 1979.

[15] Nelson, J. D., Marliss, E. B., Albisser, A. M., and Zinman, B.: Role of continuous component in subcutaneous "open-loop" insulin delivery. Lancet *1*: 1383–86, 1980.

[16] Rizza, R. A., Gerich, J. E., Haymond, M. W., Westland, R. E., Hall, L. D., Clemens, A. H., and Service, F. J.: Control of blood sugar in insulin-dependent diabetes: comparisons of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional insulin therapy. N. Engl. J. Med. *303*: 1313–18, 1980.

[17] Tattersall, R., and Gale, E.: Patient self-monitoring of blood glucose and refinements of conventional insulin treatment. Am. J. Med. *70*: 177–82, 1981.