Editorials

"Control" and Diabetic Complications

This issue of DIABETES CARE contains the first part of the English translation of an article that appeared recently in French in the journal *Diabete et Metabolisme* (vol. 3: 97–107, 173–82, 245–56, 1977) entitled "Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973," by Jean Pirart of Brussels, Belgium. The Editors of DIABETES CARE decided to publish an English translation of this article for a number of reasons. First, the study represents a monumental amount of data collected by a dedicated group laboring for more than a quarter century. We felt that such data should be brought to the attention and undergo the careful scrutiny of an English-speaking audience. Second, it is unlikely that there will appear many such comprehensive prospective studies, and therefore it is immensely important, albeit imperfect. Third, there are lessons to be learned from the Brussels experience—both in terms of study design and in terms of the implications of the results of the study.

The Brussels study doubtless will be faulted because patients were not randomly allocated to various groups in terms of degree of diabetic control. Although prospective in terms of data collection, the assignment of patients to one or another group could only be done retrospectively. Further, the criteria for "good," "fair," and "poor" degrees of glycemic control are arbitrary, and really only represent varying degrees of "poor" control. (My view is that "good" control is euglycemia.) Nevertheless, the categorization is similar to that used by others and is close to what clinicians, in general, apply. The arbitrariness of selection of criteria is not inappropriate, also, if we consider that the bottom line is that, with increasing degrees of hyperglycemia, there are more complications. Since that relationship is probably more or less linear, *where* one divides the groups isn't likely to matter. What is of concern is the unanswerable 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.

Are we justified, however, to consider attempting the study that will satisfy all critics in terms of experimental design—a prospective, randomized longitudinal study that has multiple objective end-points in terms of establishing both degree of control and severity of complications? In human subjects, I think not. During the decades required for such a study, new control criteria will doubtless emerge (e.g., the recent addition of glycosylated hemoglobin to our clinical armamentarium) which some will want to have had included from the outset. New generations of critics will not be satisfied without such information.

Moreover, I believe that there is sufficient information available on the subject to ethically preclude us from randomizing patients into a "poor" control group. Animal studies, although imperfect, do provide us with much information demonstrating that diabetic complications occur more frequently and with greater severity in animals with greater degrees of hyperglycemia.[1–2] These animals indeed have been followed prospectively and have been randomly allocated into "good" and "poor" control groups. Further, and more striking, is the animal evidence that complications of diabetes, at least at a relatively early stage, are even reversible to some degree.[3–4]

Critics will argue that this is chemically induced diabetes in animals. Yes, it does require some extrapolation to human beings. The history of science and of medicine, however, teaches us that most advances are made first in "lower" species and that one can almost invariably have a cleaner experimental design using animal models than one can have using human subjects. Additionally, such animal experimentation assures us that some other factor (genetic or otherwise) is not playing a role in the development of complications.

Furthermore, there is now abundant description of biochemical mechanisms in which metabolic pathways are

clearly influenced by the degree of hyperglycemia and/or insulin deficiency.[5–9] Although one can argue whether these biochemical mechanisms can be clearly implicated in the pathophysiology of the major complications of diabetes, they do provide us with many provocative and exciting biochemical models to explore further—both in terms of the direct roles of the known mechanisms in the pathophysiology of complications and in terms of related pathways in other tissues. For example, whereas the glycosylation of hemoglobin per se may or may not have anything to do with the pathophysiology of diabetic complications, it does provide a concrete model for alteration of both protein structure and function on the basis of ambient level of glucose.[10–13] It is unlikely that hemoglobin is unique among all body proteins in being so affected. Indeed, there is evidence emerging that several other proteins undergo similar glycosylation. The role of such glycosylation in the development of complications is not yet defined, but any process that alters both structure and function of proteins can be envisaged as having potentially powerful effects.

Finally, the Brussels study is yet another chapter in those clinical studies that invariably support the relationship between higher levels of hyperglycemia and more frequent and/or more severe complications. I have not yet seen any clinical study that shows any benefit for "poor" control.

It seems to me that the time has come to stop bickering about the desirability of good control. Rather, we should focus our attention on the best means of achieving good control, and determining the optimum degree of control required and desirable. I clearly recognize that that decision may vary with circumstances and that the degree of control attainable by conventional methods may vary somewhat among patients. Something approaching euglycemia, however, is attainable in many patients, and this should be our goal in most cases. To say that it is not attainable is to deny the documented experience of dedicated practitioners. It may indeed be hard to achieve and may require the concerted efforts of patients and professionals. It won't be easy, and attempts at attaining euglycemia will be complicated by occasional hypoglycemic episodes. But rather than have an irrational and unwarranted fear of hypoglycemia, I accept the infrequent, mild, recognizable hypoglycemic episode as both a useful educational tool for the patient (in terms of symptom recognition) and as an indication that glucose levels are close to the desirable range. (I do strive to avoid frequent, severe, nocturnal, or unrecognizable hypoglycemic episodes.) The misguided (in my view) efforts to avoid hypoglycemia at the expense of accepting hyperglycemia are not justified by any available data. It's time to stop making excuses for not achieving euglycemic control and start expending the effort in trying to do so.

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REFERENCES

[1] Engerman, R. L., Bloodworth, J. M. B., and Nelson, S.: Relationship of microvascular disease in diabetes to metabolic control. Diabetes *26*: 760–69, 1977.

[2] Howard, C. F.: Basement membrane thickness in muscle capillaries of normal and spontaneously diabetic Macaca Nigra. Diabetes *24*: 201–6, 1975.

[3] Mauer, S. M., Sutherland, D. E. R., Steffes, M. W., Leonard, R. J., Najarian, J. S., Michael, A. F., and Brown, D. M.: Pancreatic islet transplantation: effects on the glomerular lesion of experimental diabetes in the rat. Diabetes *23*: 748–53, 1974.

[4] Mauer, S. M., Steffes, M. W., Sutherland, D. E. R., Najarian, J. S., Michael, A. F., and Brown, D. M.: Studies of the rate of regression of the glomerular lesions in diabetic rats treated with pancreatic islet transplantation. Diabetes *24*: 280–85, 1975.

[5] Spiro, R. G.: Search for a biochemical basis of diabetic microangiopathy. Diabetologia *12*: 1–14, 1976.

[6] Gabbay, K. H.: Hyperglycemia, polyol metabolism, and complications of diabetes mellitus. Annu. Rev. Med. *26*: 521–26, 1975.

[7] Winegrad, A. I., and Greene, D. A. Diabetic polyneuropathy: the importance of insulin deficiency, hyperglycemia, and alterations in myoinositol metabolism in its pathogenesis. N. Engl. J. Med. *295*: 1416–21, 1976.

[8] Brownlee, M., and Cahill, G. F. Diabetic control and vascular complications. Arteriosclerosis Reviews, 1978, in press.

[9] Koenig, R., Peterson, C., Jones, R., Saudek, C., Lehrman, M., and Cerami, A.: Correlation of glucose regulation and hemoglobin A_{Ic} in diabetes mellitus. N. Engl. J. Med. *295*: 417–20, 1976.

[10] Bunn, H. F., Haney, D. N., Gabbay, K. H., and Gallop, P. M.: Further identification of the nature and linkage of the carbohydrate in hemoglobin A_{Ic}. Biochem. Biophys. Res. Commun. *67*: 103–9, 1975.

[11] Bunn, H. F., and Briehl, R. W.: The interaction of 2,3-diphosphoglycerate with various human hemoglobins. J. Clin. Invest. *49*: 1088–95, 1970.

[12] Bunn, H. F., Haney, D. N., Kamin, S., Gabbay, K. H., and Gallop, P. M.: The biosynthesis of human hemoglobin A_{Ic}. J. Clin. Invest. *57*: 1652–59, 1976.

[13] Bunn, H. F., Gabbay, K. H., and Gallop, P. M.: The glycolsylation of hemoglobin: relevance to diabetes mellitus. Science *200*: 21–27, 1978.

Sulfonylurea Drugs 1978

The proper role of oral hypoglycemic agents in our therapeutic armamentarium has been clouded by emotional reactions and heated debate that have obscured the real issues. The genesis of this debate is clearly the reports of the UGDP and the positions taken by authorities in response to those reports.[1] So much has been written about the UGDP, pro and con, that it is not particularly beneficial to belabor the question here. It is refreshing, then, to see a new approach taken to this subject—as has been done by Lebovitz and Feinglos in this