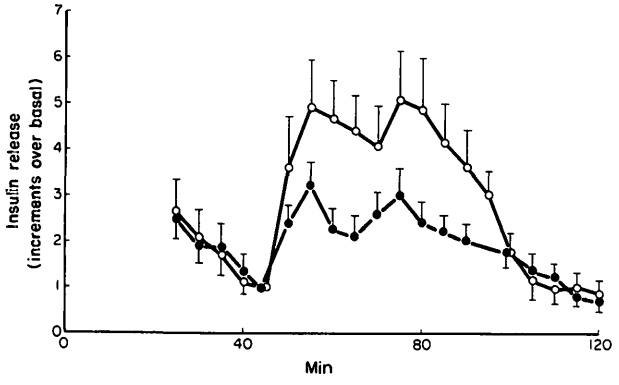

Figure 2—*Insulin release from isolated human islets perifused with different glucose concentrations and without (●) or with (○) the addition of 3.7 μg/ml metformin in the perifusion medium during the 40–80 min period.*

plus 850 mg oral metformin. The areas under the plasma glucose curve were essentially the same: 2,403 ± 155 and 2,498 ± 160 mmol at the low and high (plus metformin) dextrose dose, respectively. Plasma insulin (Fig. 1*B*) and C-peptide (Fig. 1*C*) concentrations rose higher after metformin administration. The areas under the plasma insulin curve were 25,295 ± 4,641 and 33,408 ± 6,327 pmol ($P < 0.01$) after 35 g glucose and 50 g glucose plus metformin, respectively. The values for the plasma C-peptide curves were 16.7 ± 2 and 21.0 ± 3 nmol ($P < 0.01$), respectively, without and with metformin.

In the perifusion experiments performed with 3.3 mmol/l glucose (six replicates), basal insulin release was 24.0 ± 1.4 pmol/l, and the addition of 3.7 μg/ml metformin had no significant effect on hormone output (peak value, 32 ± 8 pmol/l). In the experiments in which after 40 min of perifusion with 3.3 mmol/l glucose the concentration of dextrose was increased to 16.7 mmol/l, either with or without the addition of metformin (five replicates each), peak insulin secretion in the presence of 16.7 mmol/l glucose plus metformin (126 ± 46 pmol/l) was significantly ($P < 0.05$) higher than the peak insulin release from islets from the same pancreases at 16.7 mmol/l glucose without metformin (94 ± 31 pmol/l) (Fig. 2). Total insulin release from islets perifused for 40 min with 16.7 mmol/l glucose plus metformin was 3,640 ± 741 pmol. This value was significantly higher ($P < 0.05$) than that from islets perifused with 16.7 mmol/l glucose without metformin (2,161 ± 438 pmol).

Thus, in our NIDDM patients, after 35 g oral glucose and 50 g oral glucose plus 850 mg oral metformin, similar peripheral plasma glucose concentrations were achieved. Under this condition, a significant increase of plasma insulin and C-peptide levels was found, after metformin dosing. Although increasing doses of oral glucose per se may stimulate greater levels of insulin, possibly by enhancing gastric inhibitory polypeptide (GIP) or other gastrointestinal hormones, significant changes in maximal GIP and insulin levels after oral glucose usually occur when the glucose load increase is at least twofold (5). Conversely, metformin does not cause any significant change in GIP concentrations either fasting or after a test meal (6). Therefore, our results might be explained, at least in part, by an effect of metformin on the β-cell. Indeed, the drug significantly potentiated insulin release from isolated perifused human islets in the presence of 16.7 mmol/l glucose. Since metformin did not affect insulin release at low glucose, this might explain why the drug does not cause hypoglycemia. Although the mechanism(s) by which metformin affects insulin release is not known at this time, our results suggest that oral metformin may potentiate insulin release in patients with NIDDM, given oral glucose, and that this effect is at least in part due to a direct action of the drug on the β-cell.

PIERO MARCHETTI, MD
DAVID W. SCHARP, MD
ROSA GIANNARELLI, MD
LUCA BENZI, MD
PAOLO CECCHETTI, MD
A.M. CICCARONE, MD
PAUL E. LACY, MD
RENZO NAVALESI, MD

From the Department of Metabolic Diseases (P.M., R.G., L.B., A.M.C., R.N.), Institute of Clinical Medicine II, and Institute of Clinical Physiology of the National Research Council (P.C.), University of Pisa, Pisa, Italy; and the Islet Transplant Center (D.W.S., P.E.L.), Washington University Medical Center and Barnes Hospital, St. Louis, Missouri.

Address correspondence to Piero Marchetti, MD, Department of Metabolic Diseases, Institute of Clinical Medicine II, via Roma 67, 56100 Pisa, Italy.

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References

1. Lebovitz EL: Oral antidiabetic agents. In *Joslin's Diabetes Mellitus*. 13th edition. Kahn CG, Weir GC, Eds. Philadelphia, PA, Lea & Febiger, 1994, p. 508–529
2. Prager R, Schernthaner G: Insulin receptor binding to monocytes, insulin secretion and glucose tolerance following metformin treatment. *Diabetes* 32:1083–1086, 1983
3. Scharp DW, Lacy PE, Santiago JV, McCullough CS, Weide LG, Boyle PI, Falqui L, Marchetti P, Ricordi C, Gingerich RL, Jaffe AS, Cryer PE, Hanto DW, Anderson CB, Flye MW: Results of our first nine intraportal islet allografts in type 1, insulin dependent diabetic patients. *Transplantation* 51:76–85, 1991
4. Scharp DW, Lacy PE, Finke E, Olack BJ: Low-temperature culture of human islets isolated by the distention method and purified with Ficoll or Percoll gradients. *Surgery* 102:869–879, 1987
5. Falko JM, Crocket SE, Catalano S, O'Dorisio TM, Kramer W, Mazzaferri EL: The effect of increasing doses of ingested glucose on insulin and gastric inhibitory polypeptide (GIP) concentrations in man. *Clin Endocrinol* 13:587–593, 1986
6. Molloy AM, Ardill J, Tomkin GH: The effect of metformin treatment on gastric acid secretion and gastrointestinal hormone levels in normal subjects. *Diabetologia* 19:93–96, 1980

Response to Garber

Alan Garber's editorial in *Clinical Diabetes* (1), expressing his depression regarding the failed penetration of the educational message of the American Diabetes Association (ADA) regarding glycemic control, reminded me of

the police captain in the movie *Casablanca*, who, as he closes Rick's where gambling is openly engaged, feigns surprise and says, "I am shocked! Shocked to learn that gambling is going on here."

There is nothing new about this. The educational message has not been getting through for decades (e.g., screening and treatment of diabetic retinopathy or identification and care of high-risk feet). Dr. Garber notes many possible reasons but does not focus on the root cause—the fault lies within us.

We use mushy language (2) such as "position statement," which is defined as "an official point of view or belief of the American Diabetes Association," "recommendations," and "guidelines." Never a mandate! We are frightened by unequivocal statements because of the fickleness of science. Everything we believe is based on statistical probabilities, and we agonize about the exceptional 1 rather than the typical 99 or 999. We know the vagaries of practice, genetic variability, and patient noncompliance. We have an innate visceral dread of the malpractice implications.

But where proof of effectiveness is incontrovertible, we must stand and be counted. We should draw the line based on proven standards as the basic minimum for acceptable care of diabetic people. For these standards to be incorporated into the practice of medicine, the ADA should disseminate a simplified version to consumers (patients) and providers while providing tangible support to diabetic people who are potentially or actually harmed by failure to follow them.

Since physicians have not incorporated these standards into practices, consumers should be encouraged to insist that third-party payers, government, health maintenance organizations, and providers adhere to them or else. ADA should address the "or else . . ." as part of its mission to improve the lives of diabetic patients. This may bring confrontation. If that is the only way to move the process, we should be willing to do so for the sake of all diabetic people now and in the future.

Instead of wordy statements in the wake of the Diabetes Control and Complications Trial study (3) and its lack of impact on practice patterns, we need a militant organizational posture. Support is mounting for a similar standard of care in type II diabetes (4). The artificial, often misinterpreted, and misused separation into insulin-dependent and non-insulin dependent categories is being corrected by an ADA Task Force.

We are now able to, as the 1992 Clinton campaign did, sum it all up in a single declarative statement: It's the sugar, stupid!

ROBERT MATZ, MD

From Mt. Sinai Hospital, New York, New York.
Address correspondence to Robert Matz, MD, 32 Buena Vista Dr., Hastings-On-Hudson, NY 10706.

References

1. Garber AJ: Chronic, persistent hyperglycemia: an essential flaw in diabetes management in America (Editorial). *Clin Diabetes* 14:2–9, 1996
2. American Diabetes Association. Position Statements. *Diabetes Care* 19 (Supp. 1):S1–S52, 1996
3. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:683–689, 1993
4. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoski S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomized prospective six year study. *Diabetes Res Clin Pract* 28:103–117, 1995