Hypoglycemia due to Serum-complexed Insulin in a Patient with Diabetes Mellitus

The recent article by Albert and Popp[1] highlighted the potential for insulin antibodies to cause problems other than clinical allergy and overt insulin resistance. The case reported involved a hyperlabile insulin-dependent diabetic patient in whom presumed antibodies with heterogeneous binding affinities radically altered insulin pharmacokinetics with resultant extremes of hyper- and hypoglycemia. The origins of the clinical syndrome in that patient were presumably related to the use of impure insulins on a chronic basis with resultant antigenic stimulation and, ultimately, production of insulin antibodies. Simply switching the patient to a purified insulin, even of the beef species, resulted in gratifying clinical amelioration of the patient's hyperlabile state. In terms of using human insulin, the authors expressed the opinion that no particular advantage would be derived; however, one would anticipate that human insulin, being less antigenic than beef insulin, would result in radically lower antibody titers with enhanced long-term clinical stability. The authors' rationale for such a negative attitude toward human insulin was unclear. The reference to the different effects experienced with pork and beef insulins could be explained simply by the fact that on the morning when the pork insulin was administered, the fasting blood sugar was at least 200 mg/dl higher with no documentation of ketones, which may have contributed further to a variable degree of insulin resistance on that day. Furthermore, no direct comparisons were made with human insulin, either of the biosynthetic or semisynthetic nature. Empirically, we have been switching all hyperlabile type I diabetic patients to purified insulins in the hope of reducing antibody titers, and avoiding the potential problems documented in the study by Albert and Popp. The problems with control we have experienced in these patients have not been as intense as those of the patient of Albert and Popp, but essentially have been episodes of hypo- and hyperglycemia that appeared unrelated to diet, physical activity, and changes in insulin dosage and insulin administration sites.

It appears plausible that many type I diabetic individuals may exist with problems similar to those of the patient documented by Albert and Popp, which manifest as episodes of hitherto unexplained modest hyper- and hypoglycemia. We feel that insulin antibodies may not behave just as simple carrier proteins[2] with a stable equilibrium between the free and bound states, but may behave in a more erratic fashion with either the antibody-bound insulin exerting independent insulin action or perhaps resulting in erratic release of free insulin from the antibodies.[3] In view of the current drive toward more intensified insulin therapy and better normalization of blood sugars, we feel that antibody-related problems of diabetic control may be unmasked more frequently as clinical awareness increases. Hopefully, the more widespread use of purified, less antigenic insulins will result in lower overall antibody titers and, hopefully, the removal of one further variable in the multiplicity involved in the overall control of type I diabetic individuals.

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Hypoglycemia due to Serum-complexed Insulin: A Reply

We hope that our article (Diabetes Care 1984; 7:285–90) might be interpreted at several levels. At the first level, we were faced with a difficult clinical management situation, that of a patient with alternating hyper- and hypoglycemia. Drs. Sheehan and Sisam make valid clinical suggestions. They are correct that the patient had been on "impure" insulins since she first developed diabetes 13 yr ago. We also anticipated that porcine and human insulin would be less antigenic than bovine insulin. At the time that the subject was evaluated, human insulin was not commercially available and we tried a tolbutamide tolerance test to stimulate endogenous insulin release. There was no evidence of ketosis on any of the 3 days of insulin testing. We were also surprised that there was a biologic response to bovine insulin, with lesser responses to porcine and endogenous insulins. We did not prospectively evaluate the serum to document the titers of circulating antibodies to the three species of insulin in order to document a change in titer with switching to more purified insulins. Again at a clinical level, the patient continues to do extremely well on the purified bovine preparation. Switching this patient to human insulin has been considered, but has been logistically difficult due to physical and social problems.

A second explanation for her improved clinical control may be due to the switch from intermediate-acting insulin to regular insulin. In fact, the regular insulin seems to behave as an intermediate-acting insulin due to serum binding.

At a second level we hoped that the article might stimulate further thought regarding the biologic role of bound insulin. As researchers in the field of diabetes we are perfectly willing to accept a double standard. Insulin may be complexed to

affinity columns in biochemical experiments and be used to isolate insulin receptors. On the other hand, circulating complexed insulin is always assumed to be biologically active. Vaughan et al.[1] suggest that the antibody might serve as a reservoir for the liberation of free insulin and be beneficial, although Bolli et al.[2] note that the delay in recovery from hypoglycemia might also be due to free insulin released from insulin-antibody binding. It may be that the patient we reported was unique and had widely disparate circulating binding activities that contributed to the hyperglycemia and hypoglycemia. It may also be that insulin bound to her low-affinity antibody maintained biologic activity. We were not successful in our first attempt at developing an in vitro assay for evaluating the biologic activity of the bound insulin. We were able to measure biologic activity in the patient herself.

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Insulin Wastage

On reading the article entitled "Insulin Wastage in Ambulant Practice," which appeared in the July-August issue of DIABETES CARE,[1] I was struck with amazement and incredulity. The authors compared the amount of insulin purchased by insulin-dependent diabetic patients over the course of 2 yr with the amount they should have used based on their recommended dosage. They found an excess of the amount purchased over the amount prescribed, which they termed "wastage." The authors discuss a variety of reasons for this "wastage" focusing entirely on the type of syringe used, and the technique of insulin withdrawal from the vial.

The amazement and incredulity derive from the apparent belief of the authors that the subjects never deliberately deviated from the prescribed amount of insulin. As both an insulin-dependent diabetic person and a psychologist, it seems obvious to me that most people could not possibly follow exactly, over the course of 2 yr, the rigid regimen prescribed for diabetic individuals. This is certainly true with regard to diet.[2] Deviations in the direction of undereating are not significant since the penalty (insulin reaction) forces a remediation. But deviations in the direction of overeating are often compensated for by the administration of extra insulin. Thus, I would urge the authors to consider that the "wastage" they discovered may in part be due to their subjects "covering" additional food. I call this the "chocolate cake factor."

I also caution that acknowledgment of this behavior might be difficult to obtain without guarantees of anonymity. The medical profession reacts with such disapprobation to such admissions on the part of patients, that patients are loath to disillusion the professionals.

After years of being a diabetic patient and encountering a variety of diabetologists, I continue to be amazed at the idealism of these professionals. An assumption seems to be made that patients will do whatever is prescribed, regardless of its rigor or interminability. The reality is that diabetic patients are also people with habits and needs who are vulnerable to many more influences and pressures than this one aspect of their lives, however important this condition may be. Isn't it time that professionals recognize this truth and deal with their patients/subjects in a realistic rather than an idealistic manner?

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Insulin Wastage: A Reply

We fully agree with Dr. Damaser's statement that a realistic attitude rather than an idealistic one is the best basis for our role as advisors to diabetic patients. During diabetic summer camps we have had the opportunity to share the daily life of young adult diabetic patients, which has helped us to gain some insight into what insulin-dependent diabetic patients can do and can be motivated to do. Adjustments of life-style to a diabetic regimen are particularly complicated for many young people. One minor aspect of this is the difficulty to abstain from extra carbohydrate, the so called "chocolate cake factor."

However, the calculations from our study (DIABETES CARE 1984; 7:343–46), based on a practical test of insulin withdrawal carried out by 101 patients, show that technical factors rather than taking extra insulin account for most of the discrepancy between purchased and injected insulin, i.e., the "insulin wastage." The *daily* wastage was found to be 16.9 U of insulin (U40). Using a syringe with a separate needle (large dead space) and adjusting the insulin dose by injecting surplus insulin into the air leads to a daily measured loss of 11.6 U of U40 insulin for patients on a two-dose regimen. The figure