O UR experience with protamine insulin in the treatment of diabetes has led us to the adoption of certain concepts, which deviated strikingly from the long established fundamentals of diabetic therapy. These were that the urine be free from sugar and that the blood sugar approach the normal level. When we attempted to treat our diabetic patients with protamine insulin, using such criteria for satisfactory control, we encountered difficulties which on further experimental and clinical study led us to other conclusions. It is the purpose of this paper to present the evidence for our newly adopted point of view.

Our guiding principles in the treatment of diabetes mellitus when using protamine insulin are:

1. Maintenance of weight.
2. Freedom from all symptoms of diabetes—thirst, polyuria, frequency of urination, hunger, weakness, fatigue, polyphagia, pruritus of the genitals, (chiefly in females), and visual disturbances.
3. Absence of ketone bodies in the urine—acetone and diacetic acid.
4. Glycosuria, we felt was desirable as its presence afforded protection from reactions.

On the first three there is general agreement. The last, namely the glycosuria and its unavoidable concomitant hyperglycemia, have been extensively criticized (9).

Our observations began in 1936 when we commenced using protamine insulin in our diabetic clinic at the New York Hospital. We selected a group of our ambulatory patients and explained to them that we had a new insulin which we wished them to use. These patients were intelligent and cooperative. Since we knew nothing of the technique for the use of protamine insulin we followed Hagedorn's recommendation, that is, the use of regular insulin in the morning, and protamine insulin at night. The logic for this technique was sound, as it is well established that the moderately severe and severe diabetics have a rising blood sugar during the night even if no food is taken (18).

A slowly acting preparation appeared ideal, therefore, as it tended to counteract this nocturnal hyperglycemia. At that stage of our therapy, we made every effort to adhere to the dicta of a sugar free urine and a normal blood sugar. Those were the established and conventional criteria. All agreed. However, when we found that with one daily dose of protamine insulin our patients revealed a glycosuria, we began to supplement the protamine insulin with regular insulin hoping in this fashion to eliminate the post prandial glucose loss. We also found ourselves juggling the diets so that our patients instead of receiving their daily dietary intake in the three equal divisions, were given an unequal distribution of the calories, as recommended by some workers in the field (17, 28). In addition we advised the withholding at breakfast of foods containing immediately available sugar, such as fruit juices (29). The results of all this maneuvering were that our patients were not free from sugar at all times, and when we attempted to obtain and maintain a urine free from sugar our patients developed most alarming and prolonged hypoglycemic reactions which were extremely subtle in onset. Thus the patients were receiving multiple injections of insulin, they were burdened with additional dietary instructions and they

**Newer Concepts in the Treatment of Diabetes Mellitus with Protamine Insulin**

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lived in apprehension as reactions were unpredictable if the urine was kept sugar free. Up to this point protamine insulin was of little help to our patients, and we were keenly disappointed as our aim was one injection daily. We felt that such a procedure would permit the patient more freedom as it would obviate multiple injections and free him from the slavery of the definite time relationship between the insulin administration and his meals.

During our periods of observation, some of the patients treated with one daily dose of protamine insulin failed to report at weekly intervals as was their routine. While away they kept a record of their insulin administration and his meals.

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When they visited the clinic after a two, three or even four week absence, the reports revealed no reactions. They had to "force themselves to drink water," they enjoyed their food but the hunger was not extreme, and if it were not for the "terrible" urine tests they would not have come for a checkup. They certainly enjoyed the new freedom of one injection a day. It was most impressive to have a record of a continuous heavy glycosuria and a singular freedom from any and all the recognized clinical symptoms of diabetes. The patients were not too happy about the glycosuria, and reasonably so, as we ourselves had always pointed out to them that continuous excretion of sugar would lead to numerous dangerous complications. Such was the accepted hypothesis, it was postulated by men of reputation and authority, and we, as others, perpetuated these dicta as we neither had the experience, facts, nor the courage to challenge them. However, it was difficult to reconcile even the suggestion that patients could reveal a heavy glycosuria for weeks and yet be symptom free. Weren't polyuria, frequency and polydipsia results of a constant glycosuria? Why didn't they develop ketosis and coma? We argued that perhaps the time of the observation was insufficient for symptoms to develop and after acquainting the patients with our plans and aims, they were willing to continue on the prescribed routine. These observations were then extended for two and three months in the Out Patient Department, and since this longer period of study supported our earlier observations that the patients were symptom free and gained weight, one dose of protamine insulin, in the presence of a continuous heavy glycosuria, we decided to continue this work under the most carefully controlled experimental conditions. For this purpose Dr. Eugene F. DuBois, to whom I am most grateful for his cooperation and guidance, made two beds available in the metabolism ward of the Russell Sage Institute of Pathology at the New York Hospital. The results of these investigations were published (37, 38). Briefly, we studied two severe diabetic patients who received one dose of protamine insulin daily as well as a diet of 1640 calories composed of 75 gms. of protein, 60 gms. of fat, and 200 gms. of carbohydrate. One of the patients was given 50 units daily, the other 60. Both patients revealed practically a continuous and constant glycosuria—as high as 100 to 150 gms. in 24 hours on certain days—their blood sugars were consistently high throughout the day, yet they were amazingly free from any and all symptoms of diabetes mellitus, they maintained their weight, were in nitrogen equilibrium, and the urine was free from acetone and diaetic acid. These original data have been repeated with similar results (39). Such facts were startling and certainly unorthodox. They contradicted all established concepts, and suggested that perhaps with the use of protamine insulin a glycosuria may not be incompatible with satisfactory therapy. They further suggested that with protamine insulin there was satisfactory utilization of foodstuffs to maintain weight and nitrogen equilibrium even though sugar was excreted. Thus we reasoned that the factor of utilization was the dominant one and our entire plan of therapy was therefore designed to use a liberal diet and sufficient protamine insulin to achieve our criteria outlined above.

With this background we have extended the technique to our out-patient department where a considerable group of diabetic patients have enjoyed this method of therapy. Not only did the majority of them maintain their weight, but many gained. There were no complaints referable to their diabetes in spite of the glycosuria. They are in good health, in a state of social and economic usefulness, and infections among them are no more frequent than in the average individual. All these patients enjoy their freedom as there appeared no necessity for careful dietary measurements, and it is not necessary for them to carry their insulin and syringe with them. They administer the insulin to themselves in the morning and then put the equipment away until the following morning. These patients are not singled out as a group apart from their fellow men, and their habits of living approximated the normal.

THE ROUTINE OF THE CLINIC

When a patient is referred to us either with the diagnosis established or for diagnosis, a careful history is recorded. Then a thorough physical examination is done, Oscillometric records are made whenever indicated. A routine serological test for syphils is done, urinalysis, and in addition to the diagnostic blood sugar determination, other blood chemical constituents or morphology as suggested either from the history or clinical findings. If on the first examination, the patient reveals clinical symptoms of diabetes as well as a glycosuria and ketonuria, we urge that he enter the hospital. If, however, he does not show acetone bodies in the urine we continue the treatment in the out-patient department. The very initial step in our experience has been the assurance of the patient, as on his first visit he is quite upset. Most usually he consults us after the diagnosis has been made and he has a number of questions as to what "he heard diabetes does to people." His queries are explained as honestly as our knowledge permits, and we only dwell