GUEST EDITORIAL

This issue of Diabetes Bulletin brings you the papers presented during XIII Annual Scientific Meeting of R.S.S.D.I. in Bangalore. It covers some vital and practical aspects of Diabetes Mellitus (DM) ranging from insulin secretory mechanism, pregnancy in diabetes, atherogenic 'risk factors' to the timing and mode of insulin delivery, and monitoring control of DM.

Sharma from Bangalore has given a good review of the mechanism of insulin synthesis and secretion and factors influencing the same. The biphasic insulin response to glucose and other insulin secretagogues is well stressed. Her work on rabbits has clarified the role of hypothalamic glucoreceptors in influencing the effect of autonomic nervous system on Beta Cell. We now know, that the first phase of insulin release is virtually absent in non insulin dependent diabetes mellitus (NIDDM), even though it appears to be partially reversible[1]. This stimulatory effect of para-sympathetic nervous system on insulin release, is well illustrated in patients suffering from reactive hypoglycemia with emotional background. They are often relieved of hypoglycemic symptoms with parasympatholytic drugs. The observation that "sympathetic activity (particularly those mediated through alpha adrenergic receptors and blunting insulin release) overrides during stress", has relevance to many stressful situations and particularly `Stress diabetes' associated with acute myocardial infarction. Reversal of glucose intolerance in most of these patients in due course, is well documented.

In monitoring control of DM, reliance still is placed on glycosuria, an isolated fasting blood sugar or post breakfast sugar values. Many a time blood sugar is rarely estimated following lunch and dinner. With such inadequate data the assessment of diabetes control is not feasible. Moreover the practical problems of frequent laboratory visits, too many venesections or finger pricks by conventional technique, and cost are aIl real. The self home glucose monitoring (HGM) is also expensive. An un-intellegent and poorly educated and motivated patient cannot be delegated with the responsibility of performing HGM, pregnancy being an exception. Nor is it possible to estimate counter regulatory hormones and lipid profile frequently to monitor indirectly control of DM. The pitfalls of relying on glycosuria for correlating blood sugar values, is outlined in this issue. The limitations of different tests used to detect glycosuria and the use of HMG are also enumerated. Naturally then, one should welcome any single laboratory test that could reflect long term control of DM. The test should be simple, reliable and reasonably economical. The glycosylated hemoglobin (GHb) qualifies itself to these requirements[2]. A great advantage of this test is that it can be estimated on a blood sample drawn anytime during the day. By whatever reliable method[3] it is estimated, a value of less than seven percent, reflects a good control of DM in retrospective period of ten to twelve weeks. GHb is an excellent parameter to judge control of diabetes during pregnancy. Application of this test in other clinical situations and limitations noted are discussed by Chandalia: Its usefulness in Chronic renal failure and hemoglobinopathy associated with DM, needs

to be worked out clearly[4]. GHb is not a useful indicator to diagnose DM which develops acutely and suddenly, for there has not been sufficient time for Hb to get glycosylated. The reservation entertained with regard to the utility of GHb in the diagnosis of DM or impaired glucose tolerance (IGT) presumably of more than two to three months duration, has been set aside with the observations of Ramanakumar and Seshiah. In one thousand subjects the authors found a correlation between the levels of blood sugar and GHb in those having DM and IGT; The predictive value of an elevated GHb for the diagnosis being 98.2 percent. However this test was also normal in a significant number of subjects with known DM and IGT, and elevated in some normal subjects. So, when an individual is concerned GHb cannot be used in isolation for the diagnosis of DM. It is quite useful for mass screening of diabetes. Perhaps it has also a place for following the course of IGT.

It is well known that conventional use of insulin in treating diabetes fails to simulate the physiological secretary pattern of insulin. As a result, chronic hyperglycemia, wide fluctuations of blood sugar levels and Somogyi effect are frequent. In the light of these observation, it is inappropriate to talk on control versus chronic complications of DM.

Insulin delivery by continuous subcutaneous infusion (CSII) or intravenous infusion (CIVII) and multiple subcutaneous injections by employing various infusion techniques is more physiological, and have enabled to achieve long term normoglycemia. The state of normoglycemia has been shown to prevent the complications associated with pregnant diabetics and contribute to regression of microangiopathy[5]. In the guest lecture, Dr Weiland, presented his experience in 32 patients on CSII for a mean period of 12 months. The benefit included halt of progression of retinopathy (some of them had laser therapy earlier), improvement in motor and sensory neuropathy, reduction in GHb and improvement in erectile impotence (was it psychogenic ?). The problems of CSII are skin infection, hypoglycemia and Ketoacidosis due to malfunction of the purnp[6,7,8]. For various reasons and particularly because of prevailing socio-economic conditions in our country and lack of prompt aftersales service, the insulin pumps are useful to only small number of patients for a short period such as during pregnancy, acute complications or certain chronic complications of DM and insulin resistance. In any case the majority of insulin dependent diabetics can be managed satisfactorily at moderate cost by regular and judicious application of sound principles of management of DM. In this regard the plea of Ganeshan and Seshiah for administering insulin 30-60 minutes before the breakfast (or meal) has not come too late. Such a practice prevents post-prandial rise in blood glucose. Exercise performed prior to breakfast and the insulin prick contribute to further reduction in post prandial blood sugar rises. Excercise has been shown to increase the number of insulin receptors and their affinity to insulin.

The use of Insulin-Sulfonylurea combination in the treatment of "insulin insensitive" NIDDM by good old general practitioners is not new. A decade ago I always wondered at the rationale of such a practice. It has now been shown that Sulfonylurea drugs reduce plasma glucose concentration at least in part through extra pancreatic effects[10,11]. Experimental data indicate that these compounds potentiate the hepatic effects of insulin, inhibit hepatic glucose production, and enhance insulin mediated glucose transport into

skeletal muscle[12]. The paper from Cuttack presents 12 patients (seven were secondary Sulfonylurea failure NIDDM and five were primary failure of which four were J type diabetics) who were not well controlled despite high dose of insulin. They were treated with insulin, and Glybenclamide (20 mg daily.) The fall in insulin requirement was significant only in secondary failure NIDDM. Much smaller doses of either the first or second generation sulfonylurea in combination with reduced insulin dosage have helped to achieve satisfactory control in 'insulin insensitive' NIDDM (personel observations). The combination therapy should be reserved only to a selected group as indicated above and not be abused.

The W.H.O's analysis of "risk factors" of atherosclerosis in diabetic individuals indicate positive association between serum cholesterol and triglyceride (TG) levels and ischemic hearl disease (IHD)[13]. Ingestion of animal fat and cholesterol are associated with an increased death rate from IHD[14]. Non-vegetarian diabetics not complying to diet tend to have higher serum cholesterol, TG levels and greater predeliction to macrovascular disease compared to vegetarians. This trend is noted in 150 patients selected at random and reported in this Bulletin. This aspect needs to be studied further on a larger number of patients. A strong positive correlation has also been observed by others. The correlations is blunted by a high polyunsaturated fatty-acid (PUFA) intake[15]. Our inability to totally abolish the direct relationship between cholesterol intake and serum cholesterol perhaps as discussed by Karmaker is due to the diminution in the hypocholesterolemic effect of PUFA as a result of reduction in the activity of delta Δ^6 desaturase enzyme in DM.

In addition to a high PUFA diabetic diet reduction of hyperglycemia perse as observed by Das et al lower low density lipoprotein cholesterol and elevates high density lipoprotein cholesterol. The latter is considered to offer protection to atherogenesis. This benefit is confirmed in many insulin treated diabetics but doubtful in sulfonylurea treated patients[16].

That the tight 24 hour control of DM pays dividend has been amply illustrated by the favourable outcome of pregnancy associated with well controlled. DM. Prevalence of over 60 percent of some form of abnormal glucose tolerance in pregnancy as reported by Seshiah should prompt systematic investigations of all women with bad obstetrical history (BOH) so that diabetes is detected and treated early during pregnancy. The majority of pregnant diabetics in India belong to class A,B_1 and B_2, of modified White's classification[17]. By virtue of absence of vascular complications in these patients the prognosis for fetal survival is good. With excellent management of DM, foetal wastage is not more than five percent (personal observations). Much more important is to identify women who have had BOH in previous pregnancy and detect diabetes prior to the next pregnancy, so that euglycemia could be restored with insulin by the time of possible conception. This will hopefully prevent congenital anomalies during organogenesis which takes place before the seventh week of gestation[18].

Finally, the attention of clinicians is drawn to the description of acute motor neuropathy elsewhere in these pages. This entity while bearing some similarities to Guillain-Barre

syndrome has distinct features of its own and has not been widely recognised hitherto. It develops abruptly or over a period of two to six days in patients with a short duration DM recently escaped control. In fact glucose intolerence and motor weakness are demonstrated simultaneously in some of these patients. Prompt reversal of motor weakness in these patients following control of DM is only to be seen to be believed.

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References

1. Ward et al., Pathophysiology of Insulin Secretion In Non Insulin Dependent Diabetes Mellitus-Review. Diabetes care 1984; 491-502.

2. Burn et al., The Glycosylation of Hemoglobin. Relevance To Diabetes Mellitus. Science 1978 200:21.

3. Chandalia et al., Estimation of Glycosylated Haemoglobin By A Simple Chemical Method and Its Use In Monitoring Control of Diabetes. Jour Ass. Physician of India 1980, 28:623.

4. Mehta and Sianani, Glycosylated Hemoglobin- Editorial, Jour Ass of Physicians of India 1983, 31:65.

5. Chiasson et al., Continuous Subcutaneous Insulin Infusion (Mill Hiller Infuser) Versus Multiple Injections (Medi Jector) In The Treatment Of Insulin Dependent Diabetes Mellitus And The Effect Of Metabolic Control On Microangiopathy. Diabetes care 1~84, 7:331.

6. Schade et al., Intensive Insulin Therapy. Amsterdam, Excrepta Medica 1983:325.

7. Kruger and Whitehouse., Low Flow In CSII-Use Of Vitamin B12. Diabetes Care 1984, 7:397.

8. Colagiuri and Kotawicz., Complication of CSII. Diabetes Care 1984, 7:397.

9. Mishra, P.K. and Dandapet, N. S., Blood Glucose Response To Breakfast Taken Before And After Exercise. Diabetes Bulletin 1984, 4:39 (Abstract).

10. Fieldman, J.M. and Lebovitz, H.E., Biological Activities of Tolbutamide And Its Metabolites. Diabetes 1969, 18:529.

11. Lebovitz, H.E., Feinglos, M.N., Sulfonylurea Drugs: Mechanism of Antidiabetic Action And Therapeutic Usefulness. Diabetes Care 1978, 3:189.

12. Blumenthal, S.A., Potentiation of The Hepatic Action Of Insulin By Chlorpropamide. Diabetes 1977, 26:485.

13. West etal., The Role of Circulating Glucose and Triglyceride Concentrations And Their Interactions With Other "Risk Factors" As Determinants of Arterial Disease In Nine Diabetic Population Samples From The WHO Multinational Study. Diabetes Care 1983., 24:333.

14. Shekella etal., Diet, Serum Cholesterol and Death From Coronary Heart Disease. N. Engl. J. Med. 1981, 304:65.

15. Schonfeld etal., Effect of Dietary Cholesterol And Fatty Acids On Plasma Lipoproteins. J. Cli. Invest 1982, 69:1072.

16. Huupponen etal., Correlation of Serum Lipids With Diabetes Control In Sulfonylurea-Treated Diabetic Patients. Diabetes Care 1984, 7:575.

17. Feling P and Coustan. D., White's Classification-In Medical Complications During Pregnancy 1982., W.B. Saunders Company.

18. Mills etal., Malformations In Infants of Diabetic Mothers Occur Before The Seventh Gestational Week. Implications For Treatment. Diabetes 1978, 28:292.