

*Volume No. 6*

*Symposium On Diabetes*

***Advances in Insulin Therapy***

**S**ymposium on Diabetes is effort towards disseminating information about various aspects of diabetes. In the year 2000, topics of clinical importance were discussed and at Magnus Novo Nordisk are pleased to know about their overwhelming success.

**W**e intend to continue our endeavor to provide information to empower you to achieve our common goal of improving the quality of life our patients. The first publication of this year celebrates the insulin sage. From matching the patient (more don'ts than dos) to the only available insulin then, to choosing the appropriate insulin to match our patients' lifestyle (set free) an array of insulin and its injection devices have simplified the life of patients with diabetes of all ages.

**A**dvances in Insulin Therapy highlights the ever changing role of insulin from that of decreasing the mortality of patients with type 1 diabetes to its increasing use in type 2 diabetes in preventing and delaying complications of diabetes. Insulin clearly is the best studied and arguably the safest and most effective therapy for the treatment of diabetes.

**M**ore than ever before in the history of diabetes therapy, patients and health care providers have the necessary pharmacologic tools available to achieve near-normal blood glucose control.

**T**hrough this quarterly publication Magnus Novo Nordisk promise to bring forth more information related to the practical aspects of diabetes. We are hopeful that you will find this series interesting helpful your day to day clinical practice.

Happy reading!

## **INSULIN**

Insulin is a peptide hormone consisting of 51 amino acids, 21 of which constitute one polypeptide chain - A (acidic), and 30 of which comprise a second chain-B (basic). The two chains are linked by disulfide bonds.

Insulin is initially synthesized in the pancreatic beta cells as a large single-chain polypeptide, proinsulin, and subsequent cleavage of proinsulin results in the removal of a connecting strand (C peptide) appearance of the smaller, double-chain insulin molecule (51 amino acids residues). Insulin and the C-peptide remnant are packaged in membrane-bounded storage granules; stimulation of insulin secretion result in the discharge of equimolar amounts of insulin and C peptide and a small amount of unconverted proinsulin into the portal circulation. Because C peptide escapes hepatic metabolism, unlike insulin, its concentration provides a more precise marker of endogenous insulin secretion. The concentration of glucose is the key regulator of insulin secretion.

A number of other hormones termed counterregulatory hormones (glucagon, growth hormone, catecholamines, and cortisol) oppose the metabolic actions of insulin. Among these, glucagon and to lesser extent growth hormone have important roles in development of the diabetic syndrome.

## **METABOLIC EFFECTS OF INSULIN**

In order to understand the vital role of physiologic supplementation of insulin in both type 1 and type 2 diabetes, it is important to highlight mechanism of glucose homeostasis.

### **FASTED STATE**

After an overnight fast, low basal levels of insulin diminish glucose uptake in peripheral insulin-sensitive tissues (muscle and fat). Most glucose uptake occurs in non-insulin-sensitive tissues, primarily the brain, which because of its inability to use free fatty acids is critically dependent on glucose for oxidative metabolism. Maintenance of stable blood glucose levels is achieved by release of glucose by the liver and to a small extent by the kidney at rates (7 to 10 g/hour) matching those of consuming tissues. The hepatic processes involved consist of glycogenolysis and gluconeogenesis, with gluconeogenesis contributing about half and glycogenolysis contributing the remainder. Both play a significant role, and both depend on the balance of insulin and glucagon in the portal circulation. Reduced insulin levels decrease glycogen synthesis, which allows glucagon's effect on glycogenolysis to prevail. Glucagon also stimulates gluconeogenesis, whereas the lowered insulin promotes peripheral mobilization of glucose

precursors (amino acids, lactate, pyruvate, glycerol) and fuels (free fatty acids) for gluconeogenesis.

## **FED STATE**

Ingestion of a large glucose load triggers multiple homeostatic mechanisms that minimize glucose excursions and restore normoglycemia. These mechanisms include (1) suppression of endogenous glucose production, (2) stimulation of hepatic glucose uptake, and (3) acceleration of glucose uptake by peripheral tissues, predominantly muscle. Each depends on insulin. In the liver, a meal-stimulated increase in insulin rapidly suppresses glucose production directly and indirectly via suppression of lipolysis and limits glucose entry into the circulation at a time when it is flooded by exogenous glucose. In addition, about 30% of the ingested glucose is deposited in the liver as a result of the combined effects of hyperglycemia and hyperinsulinemia in the portal circulation. Consequently, a substantial amount of glucose is retained in the liver as glycogen. The uptake of glucose by peripheral tissues is mediated predominantly by insulin. In muscle, glucose may be used for glycogen synthesis or undergo oxidative or non-oxidative metabolism. In adipose tissue, glucose is used for the formation of alpha-glycerophosphate, which is necessary for the esterification of free fatty acids to form triglycerides. Intracellular metabolic processes are also facilitated: glycogen synthase and glucose oxidation by activating pyruvate dehydrogenase and decreasing lipolysis (free fatty acids compete with glucose for oxidative metabolism).

## **INSULIN DEFICIENCY**

Lack of insulin leads to mobilization of substrates for gluconeogenesis and ketogenesis from muscle and adipose tissue, accelerated production of glucose and ketones by the liver, and impaired removal of endogenously produced and exogenous fuels by insulin-responsive tissue, the net result is severe hyperglycemia and hyperketonemia that overwhelm renal removal mechanisms.

## **INSULIN THERAPY**

Diabetes knowledge, treatment and prevention strategies advance daily. Treatment is aimed at keeping blood glucose near normal levels at all times. Training in self-management is integral to the treatment of diabetes. Treatment must be individualized and must address medical, psychosocial, and lifestyle issues.

Lack of insulin plays a primary role in the metabolic derangements linked to diabetes, and hyperglycemia in turn plays a key role in the complications of the disease.

Insulin is necessary for normal carbohydrates, protein, and fat metabolism. People with 1 diabetes mellitus depend on exogenous insulin for survival. In contrast, individuals with type 2 diabetes are not dependent on exogenous insulin for survival. However, over time, many of these individual will show decreased insulin production, therefore requiring supplemental insulin for adequate blood glucose control, especially during times of stress or illness.

Lack of insulin production by the pancreas makes type 1 diabetes particularly difficult to control. Treatment requires a strict regimen that typically includes a carefully calculated diet, planned physical activity, home blood glucose testing, and multiple daily insulin injections.

Whereas in type 2 diabetes, treatment typically includes diet control, exercise, home blood glucose testing, and in some cases, oral medication and/or insulin. Approximately 40% of people with type 2 diabetes require insulin.

An insulin regimen is often required in the treatment of gestational diabetes and diabetes associated with certain conditions or syndromes (e.g., pancreatic diseases, drug-or chemical-induced diabetes, endocrinopathies, insulin-receptor disorders, certain genetic syndromes).

## **INSULIN RELACEMENT**

The goals of insulin therapy differ a between type 1 and type 2 diabetes. In type 1 diabetes, insulin therapy is designed to mimic physiologic daily fluctuation of serum insulin concentrations to provide for both basal regulation of hepatic glucose production and stimulation of glucose uptake after meals. In type 2 diabetes, the primary goal is to restrain hepatic glucose overproduction; the ability to effectively accelerate postprandial glucose disposal is variable, depending on the degree of insulin resistance.

Choosing an insulin requires consideration of species (human, cow or pig), an understanding of pharmacokinetics (Table–1) and method of injection (disposable, plastic syringe, pen, disposable pen, etc).

<b>Type of Insulin</b>	<b>Onset(h)</b>	<b>Peak(h)</b>	<b>Duration(h)</b>
NPH	1-4	6-10	12-20
Lente	2-4	6-12	12-20
Short-acting Regular	0.5-1	2-4	4-8
Rapid/fast-acting analogue Immediate		0.5-2	4-6

## ANIMAL INSULINS

Insulin of bovine or porcine origin were the only commercially available preparations for the first half-century of the insulin era. The amino acid sequence of the animal insulin differs from that of human insulin by one (porcine) or three (bovine) amino acid residues. The widespread commercial availability of animal insulins shortly after 1922 represents one of the great success stories of contemporary medicine. Although, the standard animal insulin is much purer than the insulin preparations of the past, most have proinsulin contents of less than 50 ppm. Beef or pork insulins labeled “purified” have less than 10 ppm proinsulin content usually 1 to 5ppm. Therapy with animal insulin has several limitations. These include allergic reactions to impurities present in formulations or the insulin molecule itself, the induction of clinically significant levels of gamma globulin which may alter the activity of the injected insulin, variable in the absorption characteristics of various commercial preparations, and the induction of a dermal reaction with resultant lipoatrophy.

In United States, patients requiring specifically to use bovine insulin (e.g., those allergic to human insulin) are allowed to import a six-month supply of bovine insulin. A few manufacturers of bovine insulin are now supplying bovine insulin to these patients on a personal use basis only. **The Cattle pancreas material used for the production of Bovine insulin is certified by the producer to come from countries recognized by the European Union as BSE-free.**

In view of concerns that BSE (bovine spongiform encephalopathy) could possibly be transmissible to man, the CJD (Creutzfeldt-Jakob Disease) Surveillance Unit was set up in 1990 to monitor the incidence of disease in the UK.

American Red Cross implemented new deferral criteria based on guidance issued by the U.S. Food and Drug Administration (FDA). The guidance, which is intended to reduce the theoretical risk of transmitting new variant Creutzfeldt Jakob Disease (nvCJD) through blood transfusion, calls for the indefinite deferral of all blood donors who have spent a cumulative time of six month or more in the United Kingdom between the years 1980 and 1996.

The cause of nvCJD is unknown, but it has linked to eating beef infected with bovine spongiform encephalopathy (BSE), commonly referred to as “mad cow disease”.

The deferral is being required because the U.S. Department of Health and Human Services, which has oversight over the FDA, believes that individuals who have visited or resided in the United Kingdom may be at risk for exposure to

nvCJD. The time considered most relevant to the BSE epidemic in the United Kingdom was between the years 1980 and 1996. Therefore the FDA guidance recommends that donors who have cumulatively spent six month or more (between January 1, 1980, and December 31, 1996) in the United Kingdom be indefinitely deferred from donating blood.

The deferral criteria also calls for the indefinite deferral of donors who received **bovine insulin** (made from cattle) since 1980, unless the donor is certain that the product was not manufactured from cattle in the United Kingdom between 1980 and 1996.

### **New Questions to be asked of Potential Blood Donors by American Red Cross**

Effective March 6, 2000, the questionnaire completed before donating blood contains two new questions related to this issue:

“During 1980 through 1996, have you spent a total time that adds up to 6 months or more in the United Kingdom? (England, Northern Ireland, Scotland, Wales, Isle of Man or the Channel Islands)”

**“Have you been injected with bovine (beef) insulin since 1980?”**

If you answer yes to these questions, the Red Cross will be required to defer you from donating blood at this time. (An exception would be if you are certain that the bovine insulin you injected was not manufactured from cattle in the United Kingdom between 1980 and 1996.)

This deferral is indefinite, which means deferred donors will only be able to donate again if the FDA decides to revise or revoke this guidance.

Creutzfeldt-Jakob Disease (CJD) is a rare neurological disease, first described in the 1920s and found worldwide. It usually presents in late middle-age with progressive dementia, and is usually fatal within 6 months. It is characterized by Spongiform changes in the brain, but this can only readily be diagnosed at postmortem.

CJD Surveillance Unit have described a distinct variant of CJD- in 10 cases, in people aged under 42 with dates of onset of illness in the last two years. This variant has not been previously recognized and is characterized by behavioral change, ataxia, progressive cognitive impairment and a tendency to a prolonged duration of illness (up to 23 months). The EEG is not typical of classic sporadic CJD. Brain pathology show marked spongiform change and extensive florid

plaques throughout the brain. As with typical sporadic CJD, symptoms in the early stage may be fairly non-specific.

These 10 cases have been carefully reviewed with respect to their clinical and pathological features, and do not appear to be explained by increased ascertainment. An iatrogenic factor has not been identified, and in the absence of any other more credible alternative, a possible explanation at present is that these cases are linked to exposure from cattle infected with BSE.

There is no simple diagnostic test or specified treatment, apart from general management of symptoms and support to patients and their families.

## **HUMAN INSULIN**

Because of the current worldwide availability of human insulin, animal insulins are now largely of historical interest. Human insulin has largely replaced animal insulins in the United States and Europe. It is also being said that the future availability of insulin is uncertain as major insulin manufacturers are switching over to human insulin due to the possibility of limitless supply of human insulin using the recombinant DNA technology.

As the human insulin produced by recombinant DNA technology is identical to that produced by the beta-cells of the Islets of Langerhans, it is less antigenic compared to the animal insulin because of their different amino acid sequence. In addition, current available human insulin preparations are of monocomponent purity i.e., they are virtually devoid of any proinsulin content. The neutral pH of the formulation may decrease the pain at injection site and also facilitates its intravenous administration and compatibility with intravenous fluids. As it is comparatively least antigenic it may evoke a minimal antibody response and thus fewer of the injected insulin will be bound to the antibodies. The free insulin being active form, human insulin has a much predictable glycemic response and less chances of unpredictable hypoglycemia (due to sudden release of insulin bound to antibodies) or hyperglycemia (due to excessive binding of insulin to antibodies).

**Human insulin is preferred for use in those initiating insulin therapy, individuals with allergies or immune resistance to animal-derived insulins, pregnant women, women considering pregnancy, and those expected to use insulin only intermittently.**

Human insulin is now the only form of insulin sold in North America and other industrialized countries.

In general the formulation of human insulin have an earlier onset. Peak and a shorter duration of action compared to animal insulin formulation.

## **INSULIN DELIVERY**

While researches research for exogenous insulin supplementation to be delivered directly to the portal circulation, today, the optimal use of available insulins and delivery devices to inject insulin subcutaneously will go a long way in providing symptomatic relief, impart sense of wellbeing, decrease mortality and prevent and/or delay both the micro-and macrovascular complications of diabetes.

For years, a large number of eligible patients were deprived of a more convenient and a less painful insulin injection. Pen injectors, both refillable and disposable together with the finest needles ever have improved the acceptability of insulin therapy without compromising on the safety and efficacy of the therapy. Also available are the Jet injectors and the Insulin Pump.

The development of injection devices like NovoLet® and NovoPen®3 has made injecting insulin much more convenient. Designed as a single compact unit, they eliminate the mixing and measuring required by traditional syringes and vials. Injection devices of this type are often referred to as insulin “pens” because they are designed to resemble an ordinary fountain pen and appear more discreet.

**Novopens picture Delivery systems such as NovoPen ® and NovoLet® make injections more convenient.**

NovoLet® is the simplest insulin injection device available. It is completely disposable and prefilled with insulin for several day’s use. Once emptied, the entire unit can be disposed of.

With insulin pen system such as NovoPen®3,you simply insert a replaceable insulin cartridge called a Penfill® cartridge. Each cartridge contains enough insulin for several day’s use. Another advance has been the development of ultra-thin, silicone coated needles such as NovoFine®. These needles are so thin they cause virtually no discomfort during injection.

## **Insulin Regimens**

Treatment regiments may be divided into conventional insulin treatment and intensive insulin treatment.

Whether the vascular and neuropathic complications of diabetes can be prevented or delayed by improved glycemic control was debated for more than a half century. The Diabetes Control and Complications Trial (DCCT), a 9 – year multicenter study involving 1441 type 1 patients aged 13 to 39 years who were randomly assigned to either intensive insulin therapy or conventional care. Intensive care consisted of three or more insulin injections per day or an insulin pump, self-monitoring of blood glucose at least four times per day, and frequent contact with a diabetes health care team. Conventional care consisted of one or more, commonly two injections of insulin mixtures pre day, less frequent monitoring, standard education, and less frequent visits. The target goals of therapy were markedly different. The intensive care group sought pre-meal blood levels of 70 to 120 mg/dL, postprandial blood levels of less than 180 mg/dL, and glycohemoglobin (HbA1C) values as close to normal as possible. In the conventional care group the goal was clinical well-being. Patients were divided into two groups: (1) a primary prevention group with diabetes for 1 to 5 years and no detectable complications and (2) a secondary intervention group with diabetes for 1 to 15 year who had mild non-proliferative retinopathy. Mean glucose levels in the intensive car group were 1.5 to 2.0 % and 60 to 80 mg/dL lower than those receiving conventional care. Intensive care reduced the development of retinopathy by 76% in the primary prevention group and the progression of retinopathy by 54%, in the secondary intervention group In addition, intensive care reduced the risk of microalbuminuria by 39%, frank proteinuria by 54%, and clinical neuropathy by 60% when compared with conventional care. The incidence of major cardiovascular events also tended to be lower, but the number of events was insufficient to provide statistical proof. At the least, intensive therapy did not pose a risk for macrovascular complications. The exponential relationship over time between the average blood glucose level as reflected by Hb A1C and the frequency with which retinopathy progressed in the intensive care group suggests that there may be no threshold level at which complications occur .The finding imply that any degree of improvement in glycemic control has benefit and that normalization is not required to slow the progression of complications.

The DCCT found that the benefits of intensive control were not without risk. The frequency of severe hypoglycemia requiring help from another person increased three-fold. Also, severe hypoglycemia often occurred without classic warning symptoms (often while the patient was asleep). Weight gain was also more common. These changes indicate that in some patients the risk of intensive therapy may outweigh the benefits. Included are patients with recurrent severe hypoglycemia and hypoglycemic unawareness, patients in whom the dangers of hypoglycemia are greater because of other coexisting medical conditions or their occupation, patients with far-advance complications, young children, the elderly, and patients who are unable or unwilling to participate in their management (e.g., self-monitoring of blood glucose). Such individuals are likely to benefit from less

aggressive therapy designed to lower glucose levels without provoking hypoglycemia. It is noteworthy that despite a higher rate of hypoglycemia, intensive care did not have any detectable long-term effect on cognitive functioning.

Although the DCCT did not involve type 2 diabetic patients, the Kumamoto study using a similar experimental design in lean Japanese patients with type 2 diabetes showed virtually identical results with intensified insulin therapy without increased risk of several hypoglycemia. More conclusive evidence that improved control of blood glucose is beneficial for type 2 diabetic patients derives from the recently completed United Kingdom Prospective Diabetes Study (UKPDS). The UKPDS recruited 5102 patients with newly diagnosed type 2 diabetes between 1977 and 1991. After 3 months of diet therapy, the 3,867 patients with fasting glucose levels between 6.1 and 15.0 mmol/L (110 to 270 mg/dL) were randomized to a more intensified regimen consisting of sulfonylurea and metformin (for obese patients only) or insulin or a conventional treatment regimen focused on symptom reduction. Patients were monitored for an average of 10 years. Although glycemic control gradually deteriorated in both groups, the intensified treatment group had lower mean Hb A1c than their conventional treatment counterparts (7.0% versus 7.9%). This modest improvement significantly reduced microvascular complications by 25% and all diabetes-related events by 12 %. A continuous relationship was noted between glycemia and diabetic complications, much the same as was seen in the DCCT. No glycemic threshold for microvascular complications was evident. The intensified treatment group also had a 16 % reduction in fatal and non-fatal myocardial infarction and sudden death. Serious adverse events were rare for each of the pharmacologic agents used in the UKPDS; only 1 death from hypoglycemia occurred in over 27,000 patient-years of intensive therapy. This result is accounted for by more severe insulin resistance and less severe defects in hormonal counter regulation in patients with type 2 diabetes.

What conclusions can be drawn from the DCCT and the UKPDS? The primary message is that “control matters.” In both type1 and type2 diabetic patients who are willing and able to actively participate in their management, the goal should be the best level of glycemic control possible without placing them at undue risk. A health care team should be in place and able to provide the resources, guidance, and support required to achieve treatment goals. A larger subgroup of type 2 patients may not be ideal candidates for tight control, particularly elderly patients with shorter life expectancy, such those with coexisting severe cardiovascular disease.

## **CONVENTIONAL INSULIN THERAPY**

During the first few years of type 1 diabetes some degree of beta cell function typically persist, which allows many patients to achieve glycemic control with less intensive effort. Because intermediate-acting insulins are not generally sustained over a 24-hours period and insulin requirements tend to increase early in the morning, most patients should start with two daily injections of mixture of intermediate- acting and rapid-acting human insulin before breakfast and dinner. Initially, the doses of intermediate-acting insulin are adjusted to optimize pre dinner an fasting glucose levels. Once this adjustment is accomplished, the doses of rapid-acting insulin are varied to optimize postprandial glucose peaks as well as pre-lunch and bedtime glucose values. Patients should inject in the same region but at different locations at the same time each day, i.e., in the abdomen in the morning to optimize insulin delivery and in the leg or buttock at night to slow absorption. Some patients may experience a brief “honeymoon” period during which beta cell function partially recovers and insulin doses need to be reduced. This improvement should not be used as a signal to reduce efforts aimed at glycemic control; optimized insulin therapy helps preserve residual beta cell function.

## **INTENSIVE INSULIN THERAPY**

Several years after the onset of type1 diabetes, residual insulin secretion typically ceases and twice-daily insulin injections no longer suffice despite control of diabetic symptoms. Optimal glycemic control requires that insulin delivery be directed toward more closely simulating the normal pattern of insulin secretion, namely, continuous “basal” insulin secretion throughout the day and night and brief increases (“bolus”) in insulins levels coinciding with the ingestion of meals. The major problem with regimens relying on twice-daily injections is that the glucose-lowering effect of pre-dinner intermediate-acting insulin is greatest at the time when requirements are lowest (i.e. 2:00 to 3:00 A.M) whereas when requirements are increasing early in the morning (i.e. 5:00 to 8:00 A.M.), insulin levels decline. The result is a tendency to nocturnal hypoglycemia and/or fasting hyperglycemia.

Successful management begins with control of fasting glucose levels. Failure to do so commonly leads to perpetuation of hyperglycemia for the remainder of the day or attempts at corrective measures with supplemental insulin that miss the mark. The therapeutic obstacle imposed by fasting hyperglycemia is best appreciated in the context of its pathogenesis, namely, glucose overproduction. Once hepatic gluconeogenesis has been activated in the morning, it is not readily suppressed by subcutaneous injections of insulin, and hyperglycemia persists after breakfast. The key factors responsible for fasting hyperglycemia are

inadequate overnight delivery of insulin and sleep-associated growth hormone release. The “dawn phenomenon” is most pronounced in patients with type 1 diabetes because of their inability to compensate by raising endogenous insulin secretion. The magnitude of the dawn phenomenon can be attenuated by designing insulin regimens to ensure that the effects of exogenous insulin do not peak in the middle of the night and become dissipated by morning. Several approaches can deal with the problem. The simplest is to use three injections, i.e., mixtures of intermediate- and short-acting insulin before breakfast, short-acting insulin before dinner, and intermediate-acting insulin at bedtime. The primary disadvantage of this approach is that meal schedules must be fixed rather rigidly. Alternative multidose regimens include (1) Ultralente (twice daily) to replace basal insulin secretion and short-acting insulin before each meal or (2) short – acting insulin before each meal and intermediate- acting insulin at bedtime. Pen injectors containing cartridges filled with insulin make multidose insulin regimens more convenient.

## **DOSAGE**

The fact that insulin therapy must be individualized cannot be overstated. Insulin type and species, injection technique, insulin antibodies, site of injection, and individual patient response difference can all affect the onset, degree, and duration of insulin activity.

*Type 1 diabetes:* For initial therapy 0.6-0.7 U/kg/d is given, 25% NPH or Lente, 75% regular. Intermediate insulin dose is changed every 48h solely on the basis of the fasting plasma glucose level. In the initiation phase the regular insulin dose for each meal is based on the postprandial glucose value from the previous day. Once the therapeutic plan is developed, alterations in the daily insulin dose are based on immediate preprandial glucose values. Alteration in the dosage may be done by 2-3 units every 3-4 days or as necessary.

*Type 2 diabetes:* A reasonable starting dose is 0.2 to 0.3 units per kilogram of body weight per day. The patient's daily glucose profile assists with further adjustments in insulin dosage. 2-4 units may alter the dose every 3-4 days if required.

## **CONCLUSION**

Implementation of modern insulin therapy for type 1 diabetes is facilitated by an understanding of normal physiology. The most important concept to remember is that any improvement in blood glucose control is associated with reduced risk of microvascular complication.

## **Expert's Opinion**

### **Dr. K. C. Samal**

Advance of human has expedited the well being of all diabetic patients those require insulins. A lifestyle change after human insulin is remarkable. The complications usually faced with the use of bovine insulin have been completely eradicated with the availability of human insulin. Human insulin has great future in preventing complications.

Cuttack

### **Dr. Anant Nigam**

There is very little doubt in everybody's mind that wherever possible human insulins should be prescribed. Of course, in a country like India. Constraints be there.

Doctor should overcome the inhibition of prescribing insulins when they are most needed because late could be too late. Patients need attention beyond only prescription of insulin. It is the correct and painless method of injection with excellent delivery systems available that could go long way in breaking the barrier.

Jaipur

### **Dr. Samar Banerjee**

Till now administration of insulin injection is not prick free but Novopen III has made it pain free. With Novopen III insulin acceptance rate and prevention or delay of complications. Patients who were on syringes administration when switched on to Novopen III usually accuse of the ignorance of certain physician and I have never seen anyone to revert back. So why not to Novopen III in all cases?

Kolkata

### **Dr. C. Munichoodappa**

Economics of the patient is important in Indian context but patient should be regular in the usage of insulin once started. The advent of human insulin & delivery devices are surely an advantage for all insulin requiring patients. Frequently changing over from one species to another is to be avoided as it leads to antibody formation. If economics of the patient allows then only human insulin should be used in all insulin-requiring patient.

Bangalore

**Dr. Apurba Mukherjee**

Insulin therapy has advanced tremendously. Its acceptance has improved amongst patients, society and also general practitioners at large. The purity of insulin has become excellent. The purified porcine as well as human insulin have become the insulins of choice now. The delivery system particularly Novopen 3 has been increasingly accepted because of less pain. Exact dosing and proven to be patient friendly really. Mixed insulins (premixed) for majority of type 2 patients after secondary failure is really all that is needed for excellent metabolic control.

Kolkata