

## **PRINCIPLES AND PRACTICE OF DIABETIC MEDICINE**

*Resume of course at Department of Diabetology, Madras Medical College & Diabetes Education & Research Centre, Apollo Hospital, Madras (November 27 to December 1, 1985)*

### **Aetiopathogenesis of Diabetes Mellitus**

*(Relation of C-peptide with profile of Diabetes Mellitus, its complications and treatment modalities)*

*M.M.S. Ahuja*

A concept for inter-relationship of various aspects of diabetes to C-peptide evaluation was presented.

Etiologically, characterization of type of diabetes (Type I, II) based on serum C-peptide content provides elaborate distinctive characteristics. The beta cell reserve as measured by C-peptide relates to the metabolic profile of diabetes. In pre-manifest Type I diabetes basal C-peptide may be normal and reduced only in the immediate post stimulating phase. In malnutrition related diabetes, C-peptide reserve is preserved and ketosis does not develop.

Vascular complications seem related to insulin content (or endogenous or provided exogenously) through its effect on myointimal proliferation.

In therapy, new innovations for euglycaemia through continuous insulin therapy aim to achieve physiological metabolic stability that can probably reduce the risk of future end-organ involvement. Transplantation of pancreas or the islet cells also aims to restore C-peptide to normalcy and thus overcome disabilities related to diabetes.

### **Many Facets of Diabetes**

*J. S. Bajaj*

There is an abysmally low level of insulin present in patients with Insulin Dependent Diabetes Mellitus (IDDM) compared to the high levels in the obese Non-insulin Dependent Diabetes Mellitus (NIDDM) patient. There had been confusion in identifying the normal level of blood glucose and that required for diagnosis of Diabetes Mellitus. The National Diabetes Data Group has now recommended uniform criteria that would be acceptable throughout the world and these have also been accepted by WHO.

HLA Studies to identify the genetic basis of IDDM and NIDDM have brought out the fact that NIDDM has more than 90% risk of diabetes when compared to

only 50% in IDDM. If the person has HLA type DR3/DR4 he runs 44.4% risk of developing diabetes mellitus, though NIDDM group has not been found to have association with I-ILA. Malnutrition related diabetes as the third category of Diabetes Mellitus has been included in the recent WEIO classification (1985). Future classification of diabetes by the year 2000 AD may refer to IDDM as insulinogenic diabetes involving chromosome-6 and NIDDM as insulinopathic involvement of chromosome-11.

### **Recombinant DNA Technology in the Future of Medicine**

*V. Seshiah and C.B. Sanjeevi*

Recombinant DNA technology (rDNA) is a new method of molecular biology, which has helped to programme cells to carry out specific functions to suit our present needs. It literally means DNA constructed from bits of DNA from different sources or exchange of a section of DNA molecules.

Searching for a single virus gene is easy because the virus has much fewer genes compared to more than 6 million in each human cell. Insulin gene, which was the first to be synthesised from rDNA technology and marketed commercially had 63 nucleotides in A chain and 90 in B chain.

The process by which exact replicas are made from DNA is called cloning. The DNA sequenced can be cut into millions of specific fragments by using enzymes called restriction endonucleases. The fragments are separated using southern blotting techniques and the required gene isolated. By using another restriction enzyme, the bacterial plasmid DNA is cut and the isolated gene is inserted.

Applications of recombinant DNA technology include (1) synthesis of proteins for therapy, (2) elucidation of structure of proteins (3) gene therapy.

Proteins for therapy include hormones such as insulin, proinsulin, growth hormone, calcitonin, glucagon, parathyroid hormone, somatomedin, etc. Plasma proteins like albumin, gamma globulin, factor VIII factor IX prothrombin, etc. Enzymes like trypsin, fibrinolysin, deoxyribonuclease, in wound healing and collagenase in orthopedic surgery, chymotrypsin in cataract removal, urokinase and streptokinase for use in myocardial infarction and tissue activator used in clotting disorders. Vaccines are also made using DNA technology, e. g. hepatitis vaccine, rabies vaccine.

Growth hormone structure and urokinase structure were elucidated by DNA technology.

In gene therapy, the defective gene is removed and replaced by a normal gene. It was successfully employed in therapy for Beta Thalassemia.

## **Tropical Diabetes**

*V C. Mathew Roy*

Tropical diabetes, commonly seen in men, affects them in the age group of 10 to 30 years.

Features of tropical diabetes are :

- 1) Pancreatic calculi.
- 2) Pain abdomen
- 3) Steatorrhoea
- 4) Protruberant abdomen which feels doughy
- 5) Cyanotic hue of lips
- 6) Bilateral parotid enlargement

Tropical diabetes can present as : (1) diabetes mellitus (DM) with pain and calculi, (2) DM with pain and no calculi (3) DM with no pain and calculi, (4) DM with calculi and no pain.

Sialogram of the enlarged parotid shows a "leafless tree appearance".

Proposed etiologies of tropical diabetes are (i) protein malnutrition, (ii) vitamin micronutrient deficiency (iii) food toxins (cassava), (iv) viral infection, (v) congenital defect of pancreatic duct.

Cassava is incriminated in FCPD type of MRDM of (WHO), endemic goitre, and tropical neuropathic ataxia.

Neuropathy is an important complication.

Treatment includes diet, insulin and surgery.

## **Secondary Diabetes**

*C. V. Krishnan*

Secondary diabetes or diabetes resulting from a known cause ranges from overt metabolic dysfunction at one end to impaired glucose tolerance on the other end. It is not associated with auto-immunity, HLA antigen and islet cell antibodies.

Insulin deficiency results from disordered hormonal homeostasis.

There can be (i) hypoinsulinemic variety with endocrine overactivity on one side and under activity on the other. (2) Hyperinsulinemic variety again, with endocrine over activity on one side and under activity on the other. (3) Rare disorders include deficient insulin receptors, antibodies to insulin receptor and hereditary neuromuscular disorders.

Carbohydrate dysmetabolism follows three stages (1) Hyperinsulinism with IGT it is intermittent and reversible, on correcting the specific endocrine disease (2) insulin lag and resistance, IGT and Beta cell defect where reversibility does not always follow treatment. (3) Full blown diabetes with permanent Beta cell damage and decreased insulin production.

### **Non-Drug Therapy in Diabetes Mellitus**

*C.V. Krishnaswamy*

The patients who would benefit from non-drug therapy are (i) NIDDM patients without complications, (ii) Maturity Onset Diabetes of Young (MODY), (iii) Gestational Diabetes Mellitus (GDM), (iv) Impaired Glucose Tolerance (IGT), (v) Offsprings of Congenital Diabetes (OCD).

The available modes of therapy are (i) Diet therapy, (ii) Organised timed physical activity (iii) Yoga (iv) Natural therapies (v) The Transcendental Meditation.

Using diet, the aim is to achieve an ideal body weight. The success of this therapy depends on understanding the individuals home eating habits, preferences, environmental set up, etc. The important factor to be kept in mind while prescribing diet is to allow flexibility rather than making it monotonous.

In one of the studies published by the author, International Diabetes Federation meeting at Vienna in 1979, diet therapy gave the best results among the different treatment groups (Diet, OHA and insulin) in 300 diabetics over a period of two years.

Physical activity is planned according to age and physique. It improves metabolism and induces a sense of well being. It enhances insulin activity on target tissues, especially in IDDM patients. Exercise in NIDDM should be moderate and planned so that the overweight patient loses weight steadily.

### **Insulin Delivery Systems**

*Lily John*

For achieving glycaemic control, a normal person requires only 20% of the beta cell function.

Factors affecting insulin delivery are (1) Type of insulin (regular or intermediate acting), pure insulin is ideal, (2) site of injection : arm, abdominal wall or thighs, (3) route of administration : subcutaneous, intramuscular or intravenous. (4) distribution of insulin in the tissues-vascular component clearance (5) interaction of insulin with other substances.

The following insulin regimens are available : (a) conventional insulin regime, (b) intensive conventional insulin regime (split and mixed), (c) continuous subcutaneous insulin infusion.

Insulin infusion pumps are portable devices of open loop system. They can be offered only to selected, highly motivated and intelligent IDDM patients who have unacceptable levels of blood glucose. Pumps are not superior to intensive conventional therapy. Their complications include infection, abscess formation, hypoglycemia and hyperglycemia.

Biostator, or the "artificial pancreas" is a closed loop insulin delivery device used mostly in research. There are a few clinical indications for its use, such as surgery in uncontrolled diabetic, during labour in pregnant diabetic and in brittle diabetics. The Japanese are working on implantable artificial Beta cell and much work is underway on islet cell transplantation as treatment of Diabetes Mellitus.

### **Hypoglycaemia**

*B.K. Sahay*

Hypoglycaemia is a condition where the blood glucose is low, generally less than 40 mg%.

The causes can be broadly classified into ( 1) those occurring after an overnight fast, (2) those occurring after meals, (3) those due to administration of insulin or oral hypoglycaemic drugs. Hypoglycaemia in children differs from that of adults in some aspects. Hypoglycaemia is most commonly due to administration of excess insulin or oral hypoglycaemic agents (OHA). Early recognition and treatment is imperative, failing which there may be irreparable consequences.

The common factors related to insulin administration are skipping a meal, usual physical activity, alterations in the dose of insulin or faulty technique of insulin administration.

Factors related to OHA include inappropriate doses without proper evaluation of diet therapy, OHA administration in patients with renal or hepatic insufficiency.

The common symptoms of hypoglycemia are yawning, weakness, tingling in the fingers, perspiration, rise in blood pressure, headache, diplopia, fainting disorientation and finally, convulsions. Persistence of hypoglycemia for over 6 hours may lead to permanent neurological damage. Hypoglycemia due to chlorpropamide may sometimes last for days.

Hypoglycemia is a medical emergency. A bolus of 25-50% glucose must be given to all unconscious patients during evaluation. Blood samples must be taken immediately before and after confirmation of hypoglycemia and the patient started on parenteral glucose. Glucagon may be tried. If hypoglycemia is prolonged, as with chlorpropamide over-dosage, careful monitoring is needed for the next few days.

Patient education goes a long way in preventing hypoglycemic episodes.

### **Diagnosis of Pre-Clinical Diabetic Retinopathy**

*Babu Rajendran*

Diabetes is the third commonest cause of blindness in India. Visual loss in diabetic retinopathy is due to changes in the macula (maculopathy) retinal vessels (background retinopathy) and in the vitreous (proliferative retinopathy).

Fluorescein angiography permits early diagnosis and classification of diabetic retinopathy and makes therapeutic considerations easier.

#### **Technique of fluorescein angiography**

Sodium fluorescein is injected into the forearm vein, and after 8-12 seconds (arm to retina time), the dye is seen in choroidal vessels as choroidal flush, followed by the dye filling the retina, capillary bed and veins, which are photographed.

Photographs are taken, illuminating the retina with blue light, which produces visual contrast of the dye in vessels, and applying a barrier filter that permits passage of light between 510-540 nm wave lengths.

#### **Interpretation**

1. State of carotid circulation-as estimated by arm to retina time.
2. Blood vessel pattern and new vessel formation.
3. Delineation of areas of retinal hypoxia or anoxia.
4. Location of fluid leakage as in maculopathy.
5. Site of photocoagulation required for therapy.

Vitreous fluorophotometry and Doppler velocimetry are methods still in the experimental stage that can be used in the study of pre-manifest diabetic retinopathy.

### **Role of Photocoagulation in Salvaging Vision in Diabetic Retinopathy**

*Chandran Abraham*

Diabetic retinopathy is present in 70% of diabetics who have the disease for more than 10 years.

Xenon arc laser can be used in photocoagulation. Blood filled areas in the retina are not treatable. Pan-retinal photocoagulation is done in proliferative retinopathy. In 82% of cases, it restores visual acuity.

Laser photocoagulation does not help when there is vitreal fibrosis.

### **Diabetic Leg and Foot Syndrome-A Surgeon's Experience**

*G. Sivakumar*

A distressing complication, the foot lesion occurs in 20 to 25 percent of diabetics, mostly NIDDM. The causes are many. Old age, retinopathy and depression may prevent patients from seeking medical attention. The important causative factors in foot ulcers are neuropathy, ischaemia and infection. Walking bare-foot also contributes.

Proper assessment of the foot lesion includes evaluation of

1. diabetic state and
2. vascular factors by clinical examination, capillary blood flow estimation, venous PO<sub>2</sub>, doppler examination and arteriography.

The foot lesions have been graded by Maggit (1972) as follows : Grade 0 : no open lesion. Grade I : simple ulcer Grade II : deep ulcer with slough. Grade III : deep abscess with osteomyelitis. Grade IV : forefoot gangrene Grade V : gangrene of the entire foot.

Treatment includes bed rest; diabetic foot lesion needs prompt therapy if the leg is to be saved. The treatment includes simple drainage, slough excision, excision of involved metatarsals, vascular reconstruction and sympathectomy, and in late stages amputations-conservative or radical.

### **End-stage renal disease in diabetics**

*M. K. Mani*

The incidence of chronic renal failure in diabetes is 7 % in Jaslok Hospital, Bombay, and 9% in south India. Usually diabetes becomes easy to control

in diabetics with renal failure because 40% of insulin secreted which is normally destroyed by the kidney, does not, in renal failure and insulin is, therefore, available for a longer time.

Glipizide is found to be more effective in renal failure because of its short duration of action and post-receptor effect.

In these patients, haemodialysis is done by using external shunt for arteriovenous communication. Patients with nephropathy, when put on dialysis have worsening of retinopathy, because heparin added to blood reaches retinal vessels and leaks into the vitreous.

Failure to thrive is seen in about 25% of patients with diabetic end-stage renal disease.

Long term peritoneal dialysis is also done. Access is good, it minimises the burden on cardiovascular system and facilitates glucose regulation when insulin is added to the dialysate. This is adaptable to home care by the use of 'Continuous ambulatory peritoneal dialysis' (CAPD). Unfortunately dialysis gives rise to hypoproteinaemia, and permits progress of retinopathy and is associated with high mortality and limited long term success.

### **History of Diabetic Medicine**

*J. R. Sankaran*

Polyuria has been described in the oldest medical text in Egypt, papyrus EBERS dated 1500 B. C.

Indian physicians in 6th century AD, tested urine, found it was sweet and so named it Madumeha. Symptoms of diabetes mellitus have been described clearly by Susruta in 5th century AD. Sweetness of urine, and polyuria and polydipsia have been described in the far-East in 3rd century AD.

The first complete clinical description of diabetes mellitus was given in 2nd century AD by Aretaeus of Cappadokia from Greece who said that in diabetes, there is melting down of flesh and limbs into urine. The flow is incessant as if like the opening of aqueducts.

Galen (131-201 AD) called it Diarrhoea urinosa.

Caelius aurelianus (5th century AD) writes about diabetes in a special chapter in his book "Acute and Chronic Diseases".

Aetius Amidinus (6th century AD) in his collection 'Tetra vivlos' considers diabetes to be a disease of the kidneys.



Avicenna (960-1037) in his work 'canon' describes collapse of sexual function and diabetic gangrene.

Thomas Willis (1674) called it 'pissing evil'.

Mathew Dobson (1766) observed that the serum of diabetics was sweet.

Chevreul (1815) showed that the sugar in the urine was glucose.

William Cullen (1710-1790) described diabetes as a malady of nervous system.

Thomas Cawley (1779) showed the association between pancreas and diabetes. Minkocski & Von Nering in 19th century described the development of diabetes in pancreatectomised dogs.

Paul Langerhans (1869) first described islets, scattered in the pancreas, which were named after him in 1893 by Laguesse.

Bernardo Alberto Houssay (1924) who showed that removal of the anterior pituitary corrected diabetes in pancreatectomised dogs was awarded the Nobel Prize in 1947.

F.G. Banting and C.H. Best isolated insulin from the panceas, in the laboratory of John Macleod in Toronto.

Aminoacid sequence of insulin was worked out by Sanger (1945-55) and the complete synthesis done by Katsoyamis. Chance (1972) discovered proinsulin and Hallas-Miller (1952) brought about the concept of lente, semi-and ultrelente insulin. Root, Schlichatkrull produced moncomponent insulin. Steinen (1972) showed the differences between human and porcine insulin.

### **Newer Insulins**

#### *C. Munichoodappa*

Newer insulins are useful and have definite indications in clinical use. The problems encountered with conventional insulin are (a) loss of potency (b) antigenicity.

The antigenicity may be due to (1) interrupted insulin therapy (2) altered amino-acid sequence (3) high molecular weight' of insulin (4) contaminants (5) additives (6) preservatives (7) zinc and (8) genetic predisposition:

To reduce their immunogenicity, insulins were purified by using Sephadex columns. The animal insulin was separated into three columns, peak-A peak-B and peak-C. The separated C-peak is termed as single peak insulin which is further purified by chromatography to derive Monocomponent insulin.

The different types of newer insulins are (1) highly purified animal derived insulin, (2) Sulphated insulin (3) human insulin. Human insulin is prepared by

enzymatic cleavage of the terminal amino acids from Beta chain of porcine insulin, or by recombinant DNA technology.

Purified insulin is identical to conventional insulin in terms of (1) suppression of hepatic glucose output (2) stimulation of peripheral glucose utilization (3) stimulation of lipogenesis in adipocytes. Human insulin differs from purified pork insulin in that it is rapidly absorbed.

Indications for the use of newer insulins are (1) insulin allergy (2) immune resistance to conventional insulin (3) insulin induced lipoatrophy (4) short term usages as during surgery or in gestational diabetes.

### **Hyperosmolar Non-Ketotic Coma (HNKC)**

*Jayakar Paul*

HNKC constitutes about 5% to 15% of all diabetic comas. The principal features of the syndrome commonly seen in the elderly are (1) dehydration (2) blood glucose >600 mg% (3) no keonaemia or ketonuria (4) no signs of severe acidosis (5) high serum osmolarity (6) stupor and coma

Many patients come with hyperglycemia hyperosmolarity, and some present with hypernatremic hyperosmolarity.

HNKC is usually precipitated by a stressful event. Patient has insufficient endogenous insulin secretion and impaired renal glucose excretion. Low endogenous insulin may be due to primary beta cell failure or secondary beta cell suppression by endogenous catecholamines. Low dose insulin therapy corrects the disorder, thus indicating that relative insulin deficiency exists and the available insulin is enough to suppress hepatic ketogenesis.

The depth of stupor parallels the increase in plasma osmolarity and not the severity of acidosis.

About 80% of patients who develop HNKC have moderate to severe renal insufficiency. The glycosuric osmotic diuresis results in more water loss when compared to electrolytes, and hypernatremia results.

The treatment includes (1) life support for the comatose patient (2) rapid rehydration (3) insulin replacement (4) replacement of electrolytes.

### **Diabetic Ketoacidosis**

*R. S. Hariharan*

#### **Definition**

Quantitative criteria for the diagnosis of Diabetic Keto-acidosis (DKA) include blood glucose value equal to or more than 250 mg%, plasma ketones more than 2 mmol/L and pH below 7.2.

### **Precipitating factors**

Principal precipitating factors of DKA are relative insulin deficiency and an excess of counter hormones viz., glucagon, growth hormone, corticosteroids and catecholamines. Vomiting and dehydration from any cause triggers excess secretion of counter hormone.

### **Clinical features**

Vomiting in a diabetic is an important pointer to impending DKA. Water and electrolyte disturbances constitute the main features of this disorder. The level of consciousness deteriorates with increasing plasma osmolality. So, dehydration, acidosis drowsiness in a diabetic herald DKA.

### **Management**

1. *Rehydration* assumes priority over insulin therapy. Rehydration lowers the blood glucose and acetone levels by promoting their excretion by the kidney. Indeed, rehydration alone accounts for 80% of the fall in blood glucose level that occurs in the first four hours of therapy. Normal saline is recommended until blood glucose level reaches 250 mg%, after which 5% Dextrose is introduced. Half normal saline is preferred if hyperosmolarity exists.

2. *A low dose insulin regimen*, viz. short acting insulin 6-10 units i.m./i.v. hourly or as a continuous intravenous infusion, until blood glucose reaches 250 mg%, followed by a 4-6 hourly dose thereafter. Short acting insulin alone can overcome the relative insulin deficiency and hence is preferred to intermediate or long acting insulin. Further, low dose insulin therapy is not associated with the development of cerebral oedema and the "disequilibrium syndrome" that was not uncommon with high dose insulin therapy.

3. *Bicarbonate replacement* is indicated when the blood pH is less than 7.1 or the respiratory rate is more than 36 per minute.

4. *Potassium replacement* is given once urine output has been established. Serial estimations of serum potassium and ECG monitoring can be used to guide potassium replacement therapy.

5. Supportive measures include Ryle's tube aspiration, antipyretics, and antibiotics if indicated.

*Monitoring* the treatment of DKA entails examination of blood glucose, urine for glucose and acetone, serum potassium, bicarbonate and pH determinations, and ECG monitoring.

### **Prevention of DKA**

1. Switching over to short acting insulin whenever a diabetic has persistent glycosuria and hyperglycaemia.
2. Prevention of stress hormone excess by prompt administration of antipyretics or antibiotics when indicated.
3. Prevention of dehydration and vomiting. Above all, a high index of suspicion in any diabetic who is ill, tests for glucose and acetone in blood and urine and early institution of therapy are important.

### **Receptors in Diabetes Mellitus**

*V.S. Ganesan*

Receptors are glycoprotein moieties located on the cell surface or on cytoplasmic organelles, that recognise a hormone or drug and then initiate cellular events. They may be found on (i) the cell membrane, e.g. peptide hormone receptor (ii) the cytoplasmic organelles, (iii) in the nucleus.

Insulin receptors are globular glycoprotein masses made up of four subunits. The molecular radius is 7 nm and each unit is linked to the other by disulfide bridges. The hormone-receptor complex enters a pit on the plasma membrane and is internalised by lysosomes. The Golgi apparatus degrades the complex and recycles the receptors. New receptors are synthesised in the rough endoplasmic reticulum. Coupling of the hormone with the receptor inversely determines the further synthesis of receptors.

### **Receptor dynamics**

Negative co-operativity refers to the reduction in affinity of receptors when the surrounding receptors are occupied by hormone.

Spare receptors refers to the maximum biological action that is seen even when only 10-30 % of the receptors are occupied.

Down regulation is meant the ambient insulin concentration inversely determining its own receptor number.

### **Receptors in health**

There is a diurnal variation in receptor affinity, with a peak at 10 : 00 p.m. Exercise increases the affinity and follicular phase of menstrual cycle reduces the affinity. Insulin resistance seen in normal pregnancy may be related to the receptor dynamics at the placental fetal level.

## Receptors in disease

In impaired glucose tolerance and non-obese diabetics, insulin resistance is clearly attributable to reduced insulin receptors. In obese NIDDM with fasting hyperglycemia, post-receptor events determine the severity of glucose intolerance-an acquired defect corrected by intensive insulin administration. Extremes of insulin resistance like type B syndrome with acanthosis nigricans have been documented where anti-receptor antibodies block the action of endogenous insulin.

## Oral Hypoglycemic Agents

*Ravi Nagarajan*

Two classes of oral hypoglycemic agents, namely, sulphonylureas and biguanides, are used extensively to treat Diabetes Mellitus. Sulphonylureas act mainly by releasing insulin from the beta cells of the pancreas. In addition, action of released insulin is potentiated by reducing degradation of insulin in the liver and by inhibiting gluconeogenesis. Sulphonylureas also increase receptor and post-receptor kinetics of insulin. Second generation sulphonylureas have an antithrombotic effect also. Biguanides do not release insulin. They lower blood sugar level by interfering with oxidative phosphorylation, inhibiting carbohydrate absorption from the gastrointestinal tract and increasing the peripheral utilisation of glucose. Biguanides also enhance receptor and post-receptor effects of insulin.

## Pharmacokinetics

Sulphonylureas differ in their absorption, metabolism and excretion. Genetic factors seem to play an important role in their metabolism. There is a 20 fold variation between individuals in the plasma concentration of these group of drugs. A brief summary of these characteristics is given below :

### I Generation Sulphonylureas :

<i>Name</i>	<i>Daily dose</i>	<i>Duration of action</i>	<i>Half life</i>	<i>Metabolism</i>
Tolbutamide	0.5-3 gm/day divided dose	6-12 hrs.	4-5 hrs.	Oxidised in liver and excreted in urine as inactive carboxytolbutamide
Acetohexamide	0.25-1.5 gm/day single/divided dose	12-20 hrs	6-8 hrs	60 % reduced to hydroxyhexamine which is 2½ times more potent. Undergoes renal tubular secretion.

Chlorpropamide	0.1-0.5 gm/day single dose	Upto 60 hrs.	35 hrs.	Excreted unchanged by the kidneys
Gliquidone	45-180 mg/day Divided	2-4 hrs	1-2 hrs	Hepatic

## II. Generation Sulphonylureas

Glibenclamide	2.5-20 mg/day single/divided dose	12-24 hrs	6-12 hrs	Hepatic
Gliclazide	80-320 mg/day single/divided dose	10-20 hrs	12 hrs	Hepatic
Glipizide	5-40 mg divided/ Single	10-16 hr	3-5 hrs	Hepatic No active polar metabolite; hence no accumu- lation.

## Biguanides

Phenformin	25-150 mg/day t.d. 50 mg. twice daily	4-6 hrs		Hydroxylated in liver
Metformin	1-3 gm/day divided dose sustained release 850 mg.	2-4 hrs	12-20 hrs	
Buformin	50-300 mg.			

## Sexual dysfunction in diabetes

*T.V. Kumar*

Sexual dysfunction is a common complication in male diabetics. The prevalence varies between 35 and 50%.

The causes may be psychogenic, metabolic, neuropathic and angiopathic, operating singly or together.

Clinically, two distinct types of sexual dysfunction have been identified. One is the reversible type, which may occur during metabolic crises or due to the debilitating nature of the illness. The second is a progressive, irreversible type, distinctly termed as "diabetic impotence". Erectile dysfunction of varying severity occurs commonly in diabetics, whereas ejaculatory disturbances are less common. Libido is usually unaffected.

Clinical evaluation must be aimed to identify the real problem in the patient and to find out a possible cause of the sexual dysfunction. A detailed sexual history, followed by clinical examination can identify the cause of sexual dysfunction.

A simple bedside test, the "Stamp test" for assessing nocturnal erection can differentiate psychogenic from organic dysfunction. Many of the available, non-invasive investigations help to identify the exact cause of the dysfunction.

A step care approach in management is advocated.

Current surgical methods like implantation of penile prosthesis, either semirigid, rigid or implantable prosthesis give hope to the impotent diabetic who may have otherwise lost all hope.

### **Brain and gut peptides in diabetes mellitus**

*S. Venkataraman*

Studies in the last few decades have examined the role of gut and neural peptides in the pathophysiology of Diabetes Mellitus. The cells of origin of these peptides have been called the third sub-division of the autonomic nervous system. The term enteroinsulin axis was coined by Unger and Eisentraut in 1969. Of the many peptides, gastric inhibitory polypeptide (GIP) contributes significantly to this axis. The negative feedback control exerted by GIP on insulin release is lost in obesity, and accounts for the hyperinsulinaemia. The peptides GLI (Gut glucagon like immunoreactivity) and neurotensin, that enhance insulin release, are probably responsible for reactive hypoglycemia. The study of heroin addicts who exhibit defective insulin response to IV glucose (an effect similar to that seen in NIDDM) offers a good model to establish the role of endogenous opiates in the pathophysiology of NIDDM. It has been suggested that NIDDM could be a manifestation of increased sensitivity to endogenous encephalins.

Further research is needed to delineate the precise role of these peptides in the pathophysiology of Diabetes Mellitus.