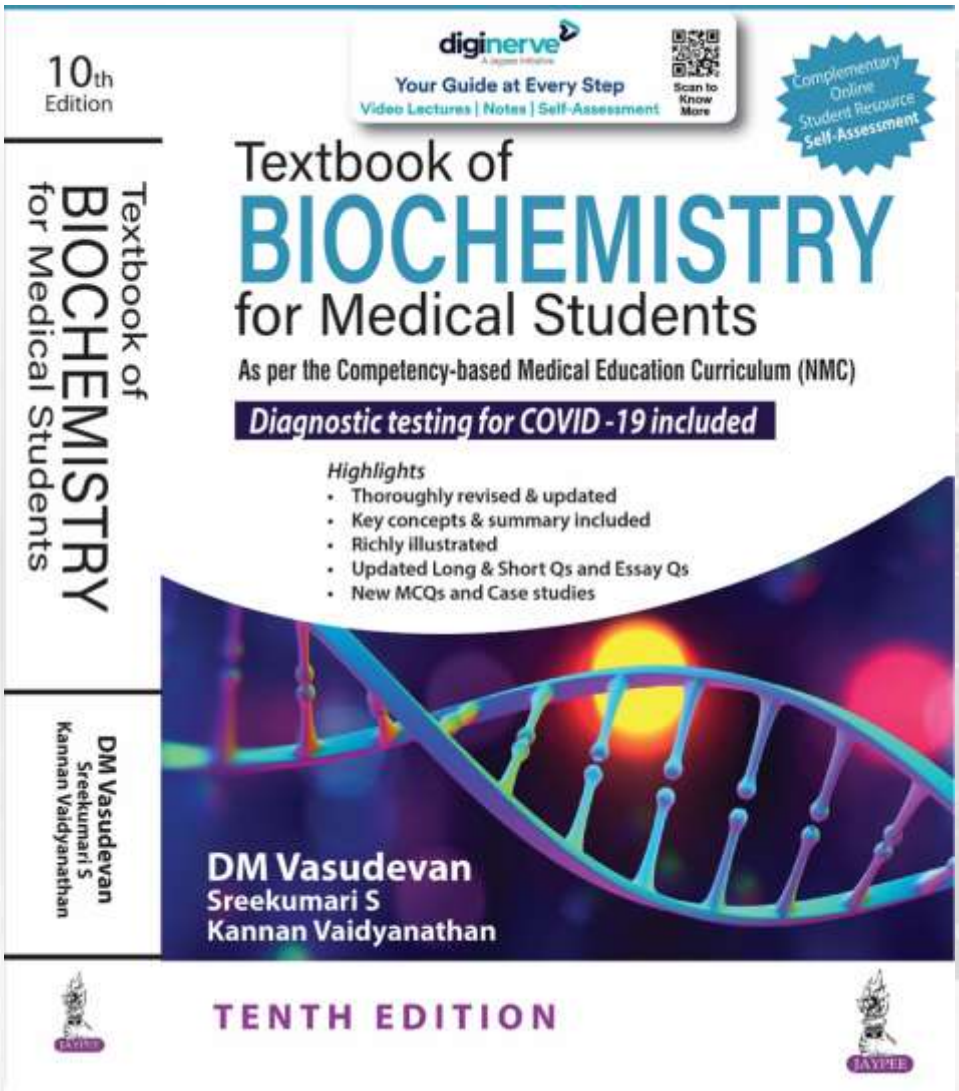


Chapter 9:

BLOOD GLUCOSE REGULATION, INSULIN, DIABETES MELLITUS

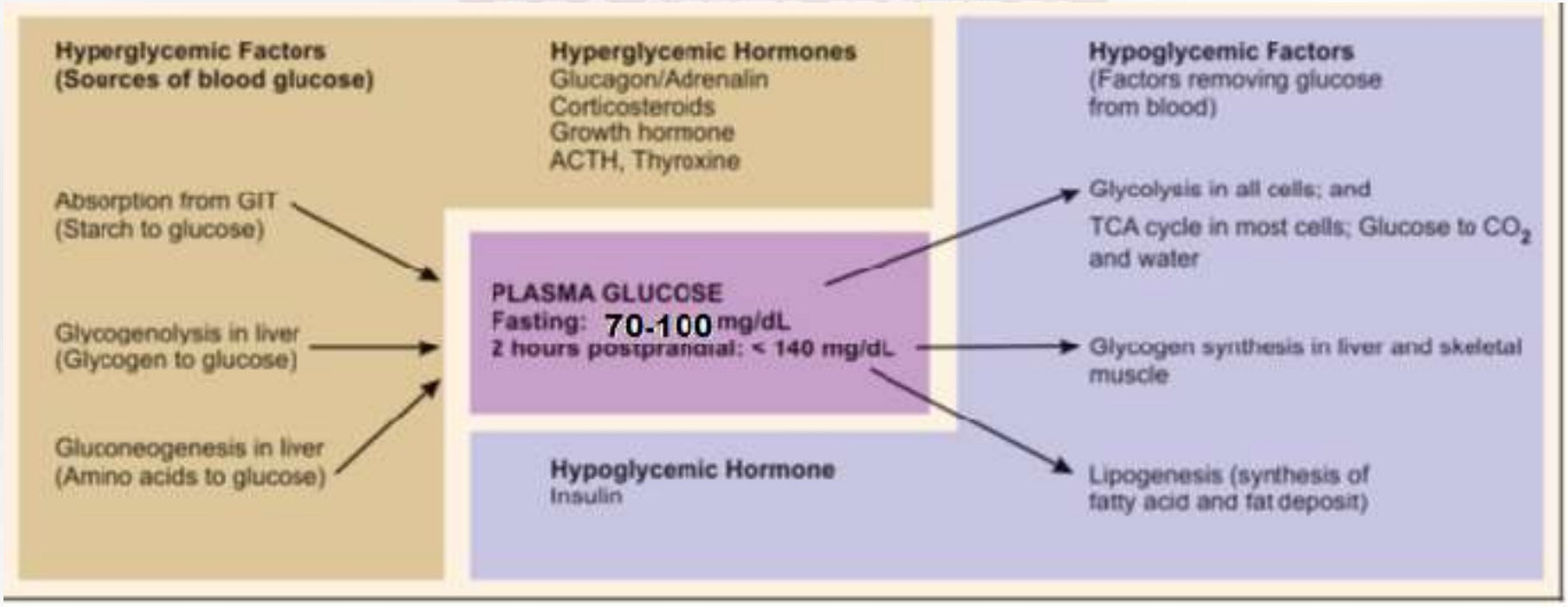
Textbook of
BIOCHEMISTRY
for Medical Students

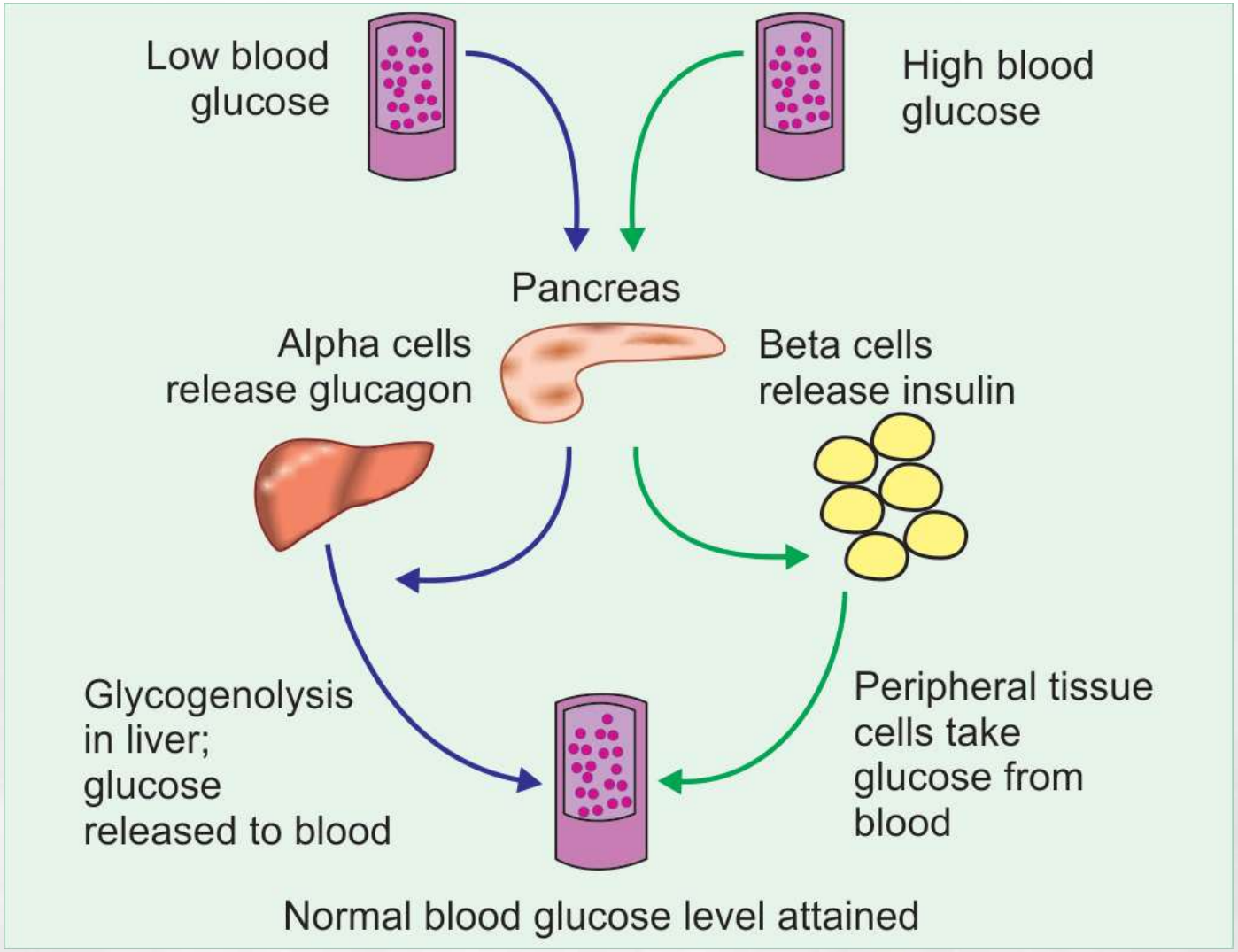
By DM Vasudevan, *et al.*

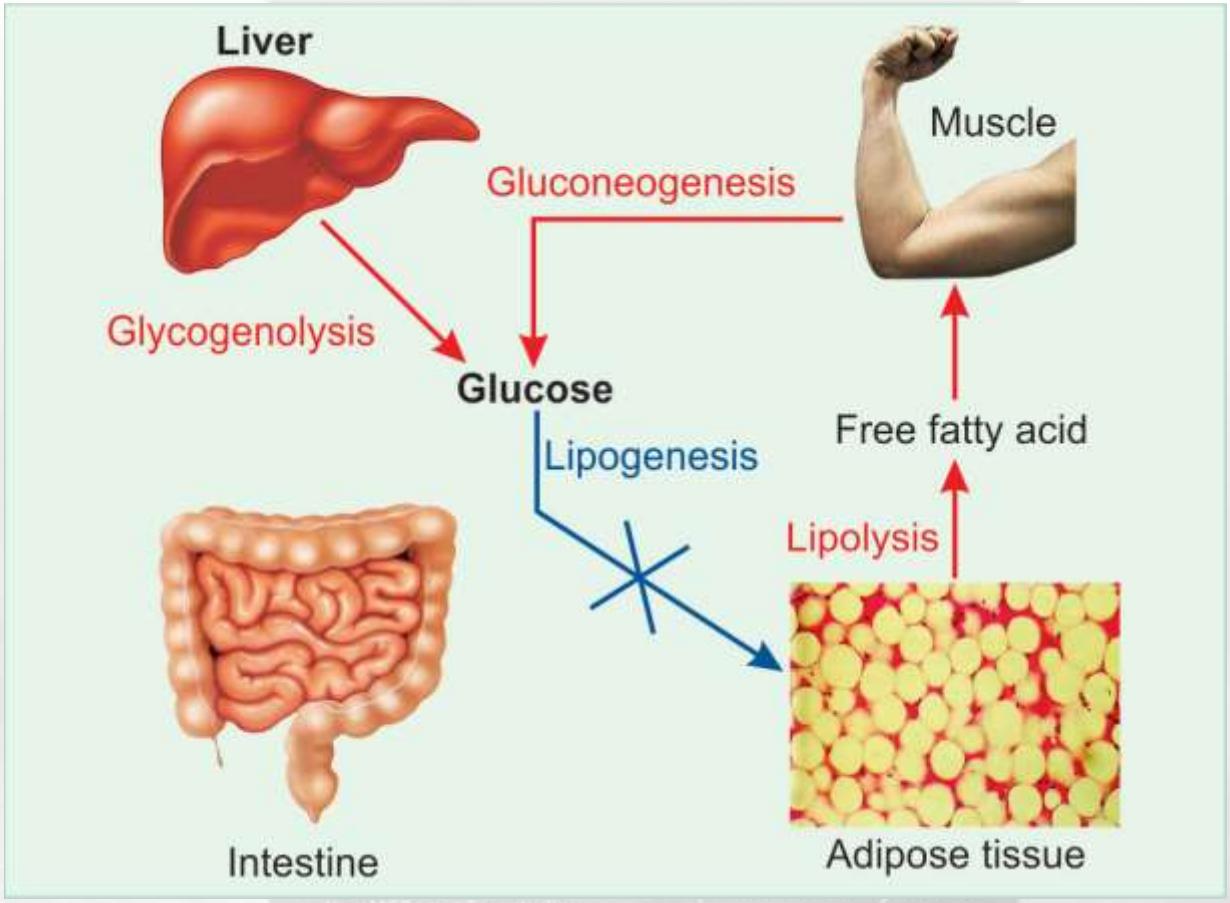
TENTH EDITION

It is essential to have continuous supply of glucose to the brain.

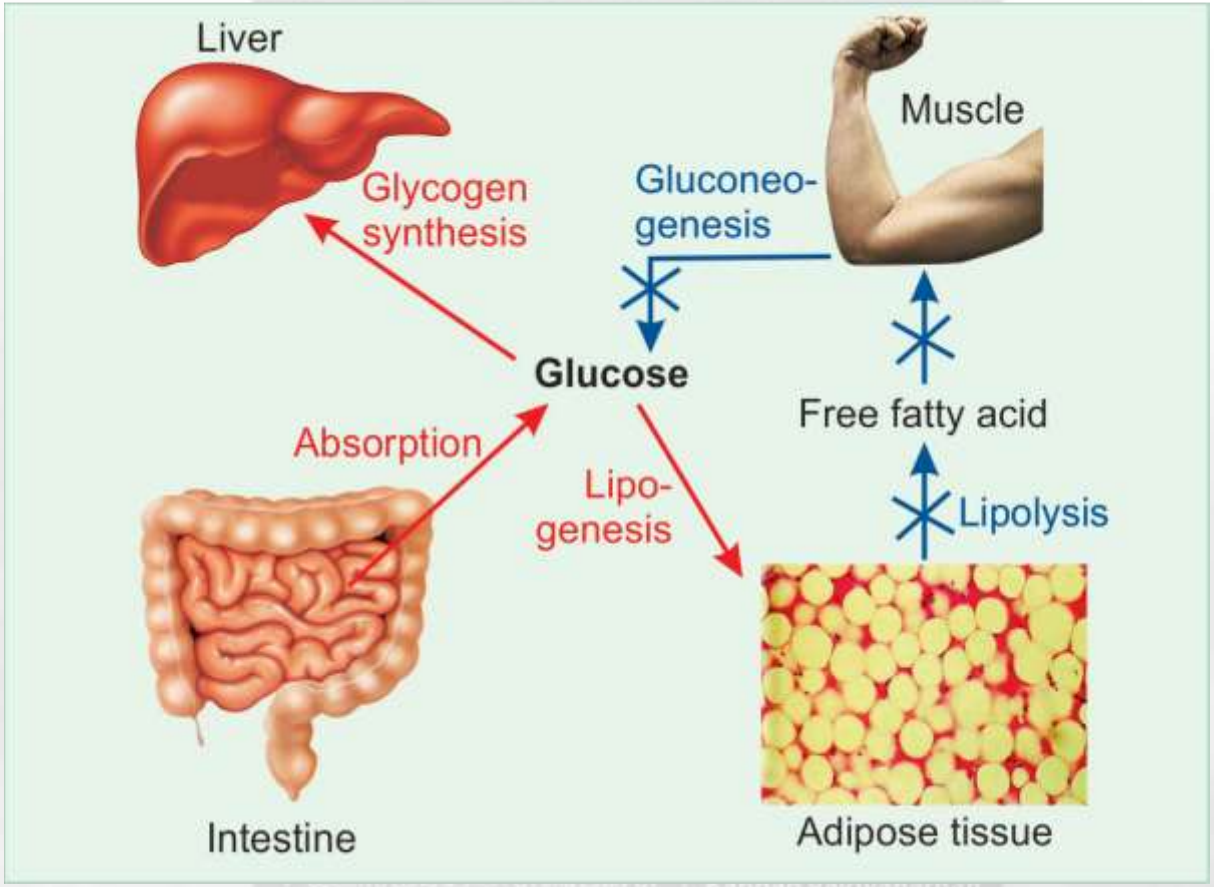
Brain has an obligatory requirement for glucose




Low blood glucose
High blood glucose
Pancreas
Alpha cells release glucagon
Beta cells release insulin
Glycogenolysis in liver; glucose released to blood
Peripheral tissue cells take glucose from blood
Normal blood glucose level attained



Blood glucose regulation during fasting state (high glucagon). Red arrows indicate activation; blue arrow indicates inhibition.



Blood glucose regulation during postprandial state (high insulin). Red arrows indicate activation; blue arrow indicates inhibition.

Effects of Hormones on Glucose Level in Blood

A. Effect of insulin (hypoglycemic hormone)
   1. Lowers blood glucose
   2. Favors glycogen synthesis
   3. Promotes glycolysis
   4. Inhibits gluconeogenesis

B. Glucagon (hyperglycemic hormone)
   1. Increases blood glucose
   2. Promotes glycogenolysis
   3. Enhances gluconeogenesis
   4. Depresses glycogen synthesis
   5. Inhibits glycolysis

Effects of Hormones on Glucose Level in Blood

C. Cortisol (hyperglycemic hormone)

1. Increases blood glucose level
2. Increases gluconeogenesis
3. Releases amino acids from the muscle

D. Epinephrine or adrenaline (hyperglycemic)

1. Increases blood glucose level
2. Promotes glycogenolysis
3. Increases gluconeogenesis
4. Favors uptake of amino acids

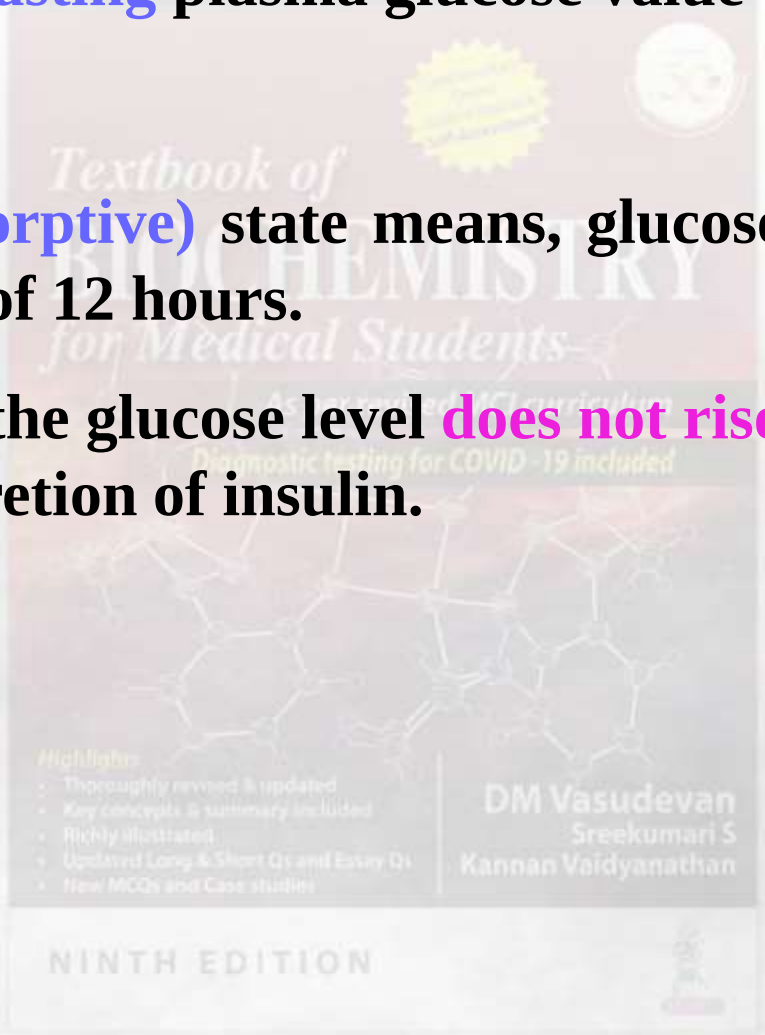
E. Growth hormone (hyperglycemic)

1. Increases blood glucose level
2. Decreases glycolysis
3. Mobilizes fatty acids from adipose tissue

Normal persons, fasting plasma glucose value is 70–100 mg/dL

Fasting (post-absorptive) state means, glucose is estimated after an overnight fast of 12 hours.

Following a meal, the glucose level does not rise above 140 mg/dL due to prompt secretion of insulin.



Normoglycemia = blood glucose level is within normal limits

Hyperglycemia = values are above the normal range (Greek, hyper = above).
Hyperglycemia is **harmful**

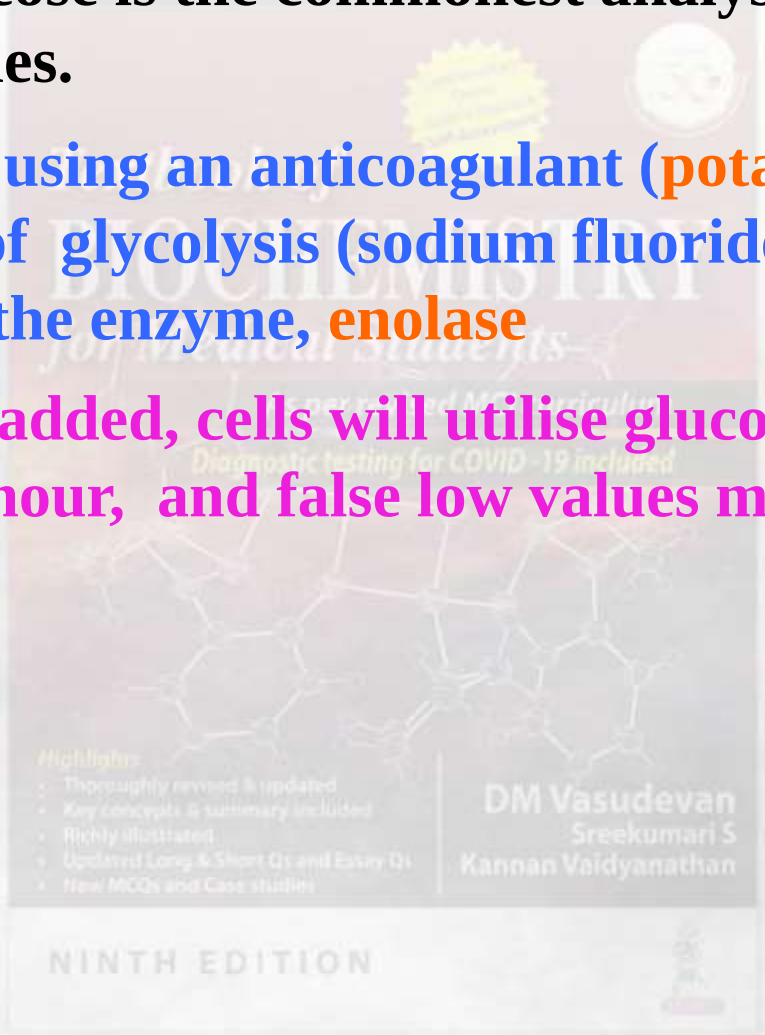
Hypoglycemia = the value falls below normal levels. (Greek, hypo = below).
If it is below 50 mg/dl, it may be **fatal**.

Determination of Glucose in Body Fluids

Estimation of glucose is the commonest analysis done in clinical laboratories.

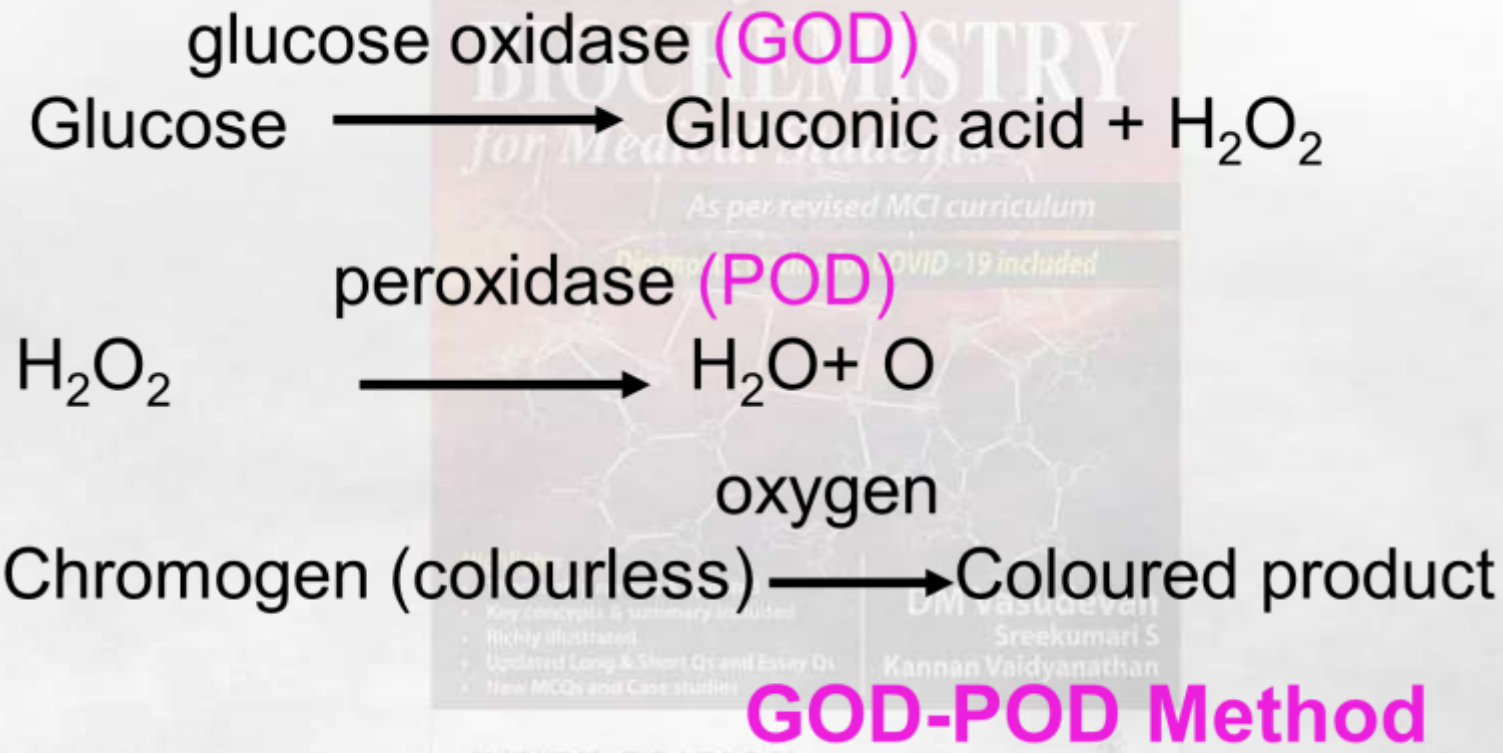
Blood is collected using an anticoagulant (potassium oxalate) and an inhibitor of glycolysis (sodium fluoride).
Fluoride inhibits the enzyme, enolase

If fluoride is not added, cells will utilise glucose at the rate of about 10 mg per hour, and false low values may be obtained.



Enzymatic Method

Highly specific, giving 'true glucose' values (fasting 70–100 mg/dL)



GOD-POD Method

GOD reaction mixture is immobilised on a plastic film (dry analysis). One drop of blood is placed over the reagent. Colour is developed within one minute.
The intensity of dye is measured by reflectance photometry.

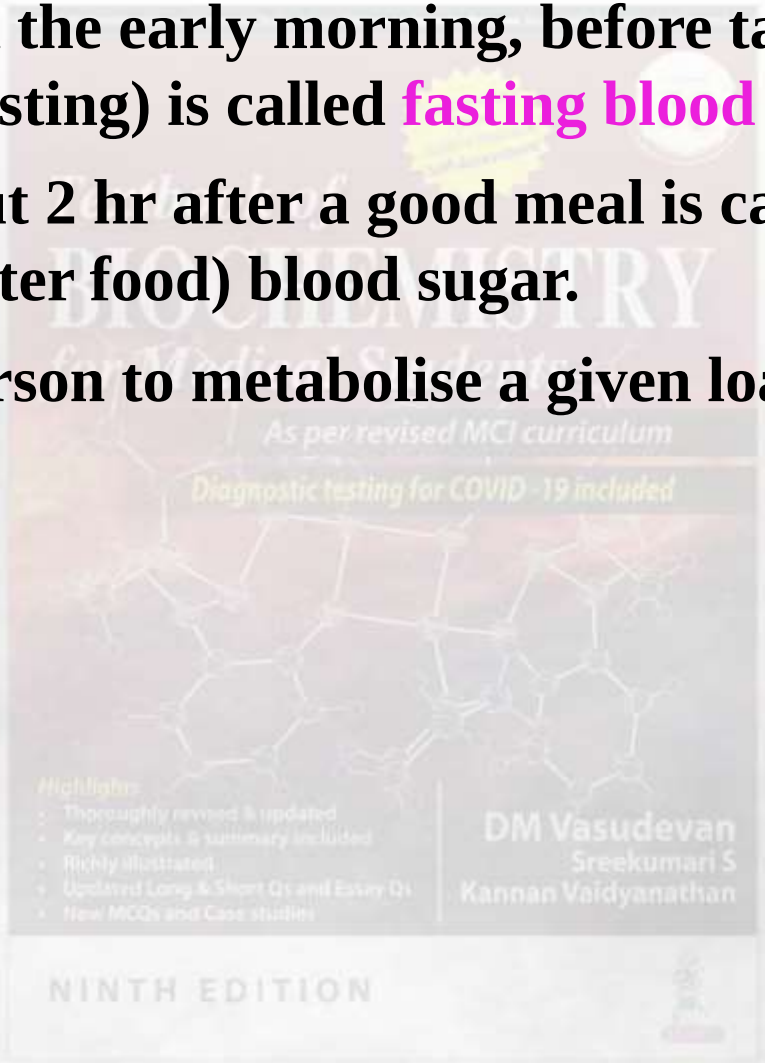
The instrument is named as glucometer. This is the best choice when quick result is needed. It is also useful for patients to have self-analysis at home. Disadvantage is that the instrument is less accurate

Blood sugar analysed at any time of the day, without any prior preparations, is called random blood sugar.

Sugar estimated in the early morning, before taking any breakfast (12 hr fasting) is called **fasting blood sugar**.

The test done about 2 hr after a good meal is called **post-prandial** (Latin, after food) blood sugar.

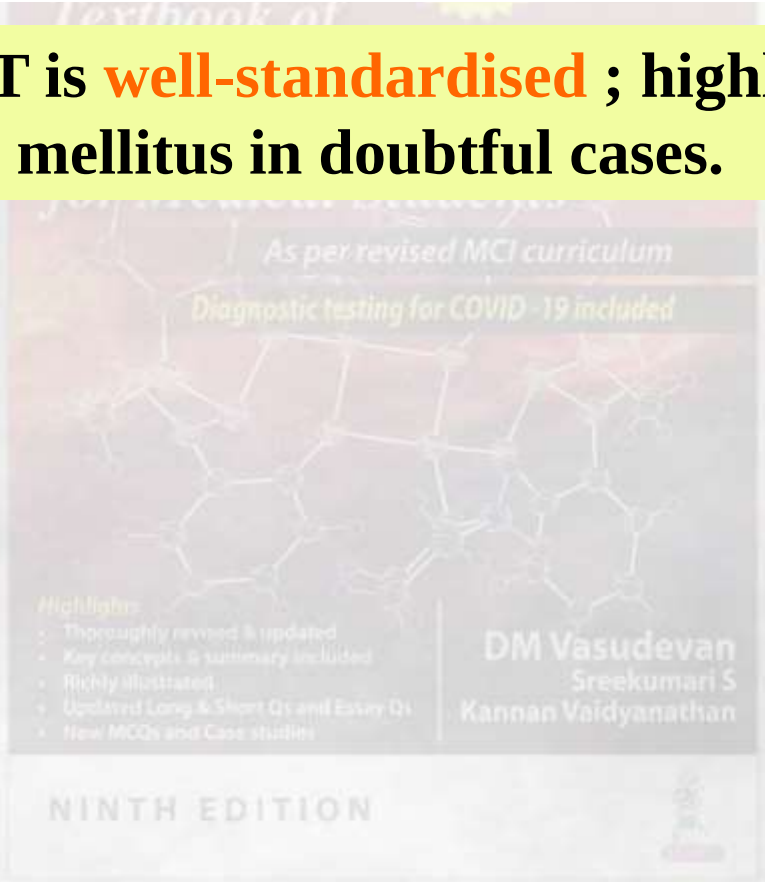
The ability of a person to metabolise a given load of glucose is **glucose tolerance**.



Oral Glucose Tolerance Test (OGTT)

It is artificial, because in day to day life, such a large quantity of glucose does not enter into blood.

However, the GTT is well-standardised ; highly useful to diagnose diabetes mellitus in doubtful cases.



Preparation of The Patient

The patient should have good carbohydrate diet (more than 150 g carbohydrate) for 3 days prior to the test.

This is important

Otherwise carbohydrates may not be tolerated even in a normal person.

Patient should not take food after 8 PM the previous night. Should not take any breakfast. This is to ensure 12 hours fasting.

The patient must be made comfortable and should be seated during the test.

Patient is asked to come early in morning, without any breakfast Blood and urine sample collected at 0 hr

Glucose Load

Give glucose solution to drink.

Dose: 75 g anhydrous glucose (82.5 g of glucose monohydrate) in 250-300 ml of water.

In children, glucose dose 1.75 g /kg body weight.

Sample Collection

½ hour intervals for next 2½ hours.

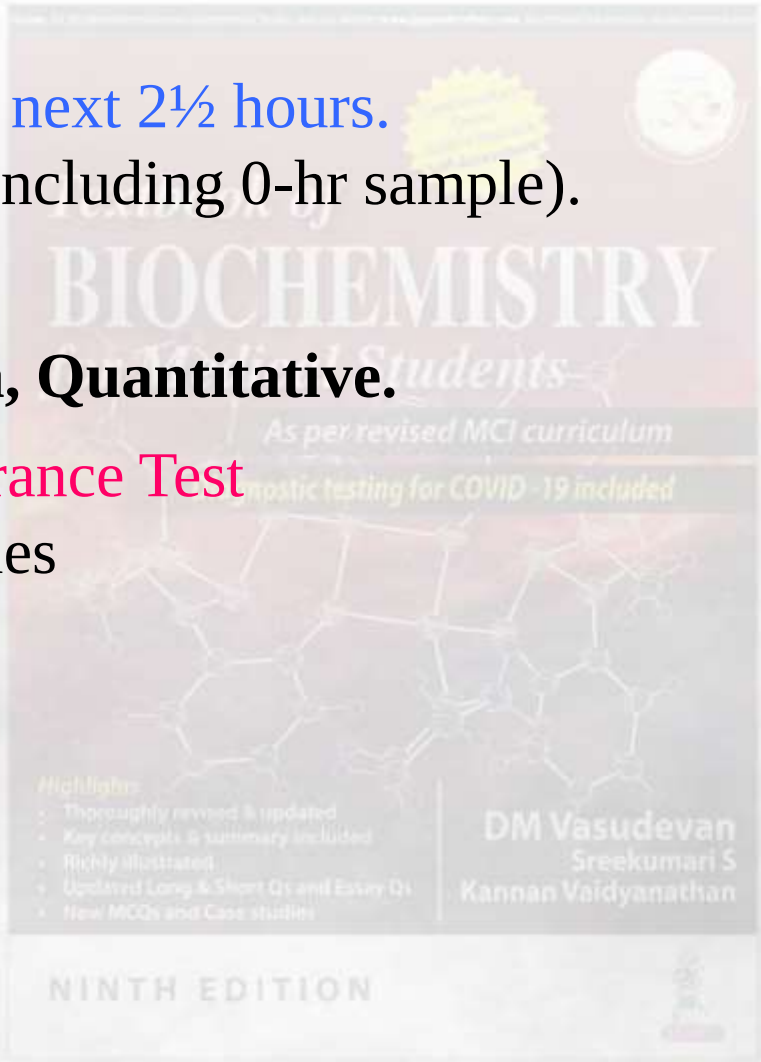
(Total six samples, including 0-hr sample).

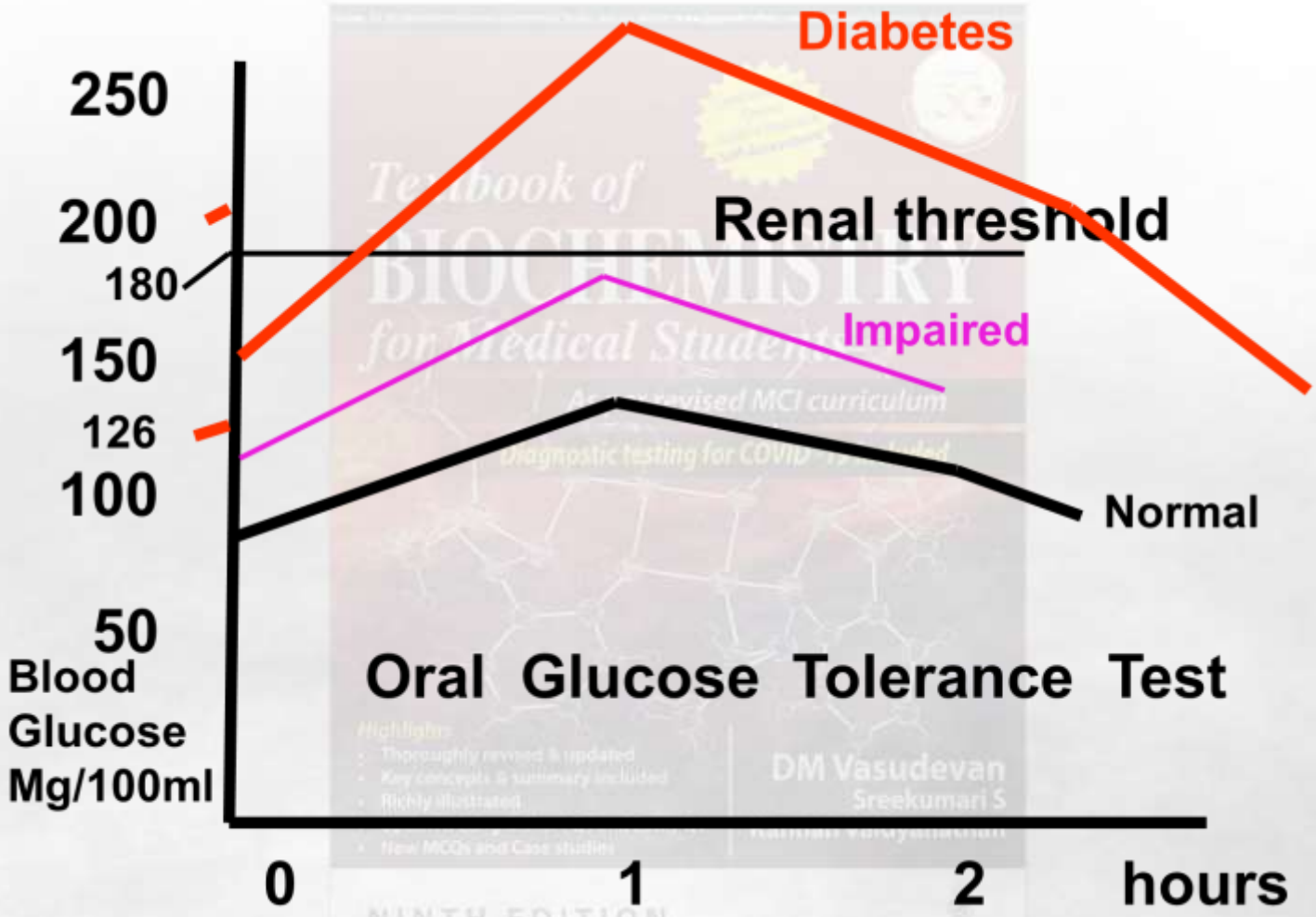
Blood samples,

Glucose estimation, Quantitative.

Mini Glucose Tolerance Test

0 hr and 2 hr samples




Diabetes
250
200
Renal threshold
180
Impaired
150
126
100
Normal
50
Blood
Glucose
Mg/100ml
Oral Glucose Tolerance Test
0
1
2
hours

Plasma Glucose Levels in OGTT in Normal Persons and in Diabetic Patients

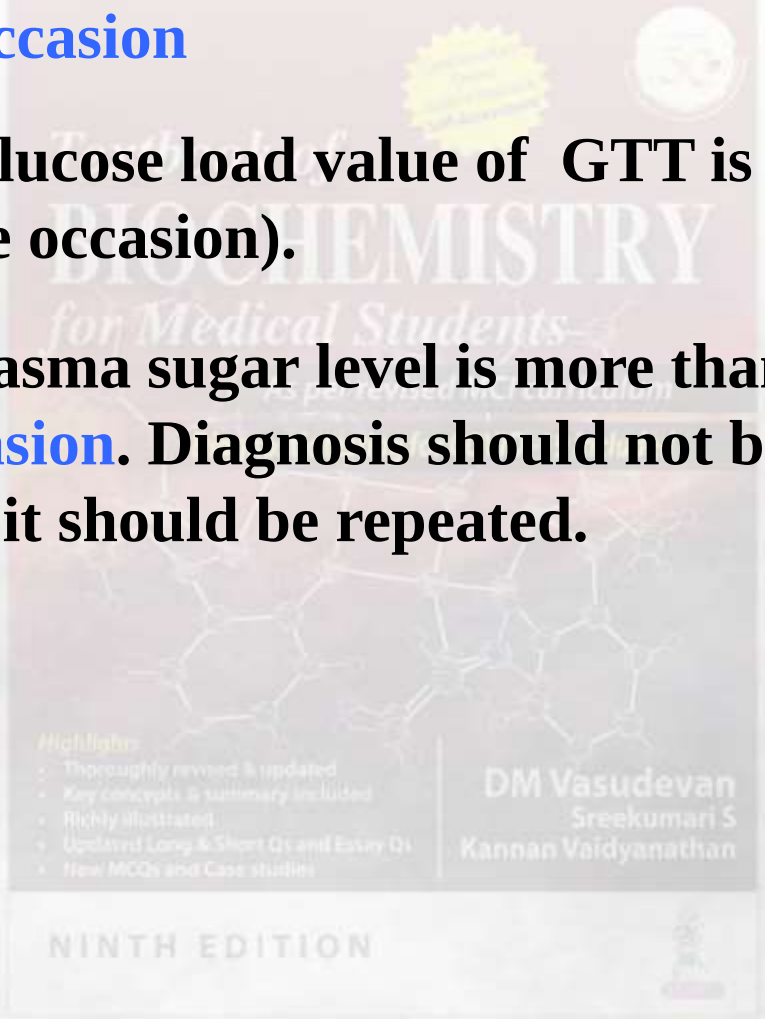
	Normal Persons	Criteria for diagnosing diabetes	Criteria for diagnosing IGT
Fasting	< 100 mg/dL	> 126 mg/dL	101 to 126 mg/dL
1 hr (peak) after glucose	< 160 mg/dL	Not Prescribed	Not Prescribed
2 hr after Glucose	< 140 mg/dL	> 200 mg/dL	141 to 199 mg/dL

Diagnostic Criteria for Diabetes Mellitus

1. If the fasting plasma sugar is more than 126 mg /dL, on more than one occasion

2. Or, if 2-hr post-glucose load value of GTT is more than 200 mg /dL (even at one occasion).

3. If the random plasma sugar level is more than 200 mg/dL, on more than one occasion. Diagnosis should not be based on a single random test alone; it should be repeated.

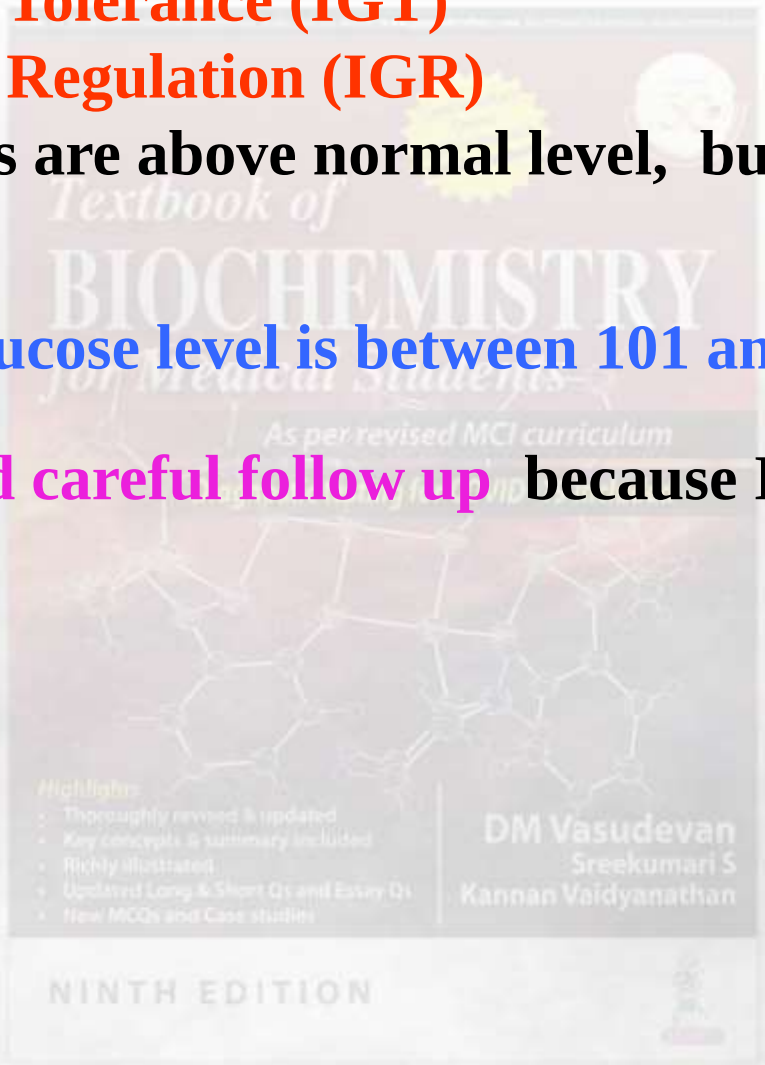


Impaired Glucose Tolerance (IGT)
Impaired Glucose Regulation (IGR)

Blood sugar values are above normal level, but below the diabetic levels.

Fasting plasma glucose level is between 101 and 126 mg/dL

Such persons need careful follow up because IGT progresses to frank diabetes



Gestational Diabetes Mellitus (GDM)

carbohydrate intolerance is noticed, for the first time, during a pregnancy.

A known diabetic patient, who becomes pregnant, is not included in this category.

increased risk for subsequent development of frank diabetes.

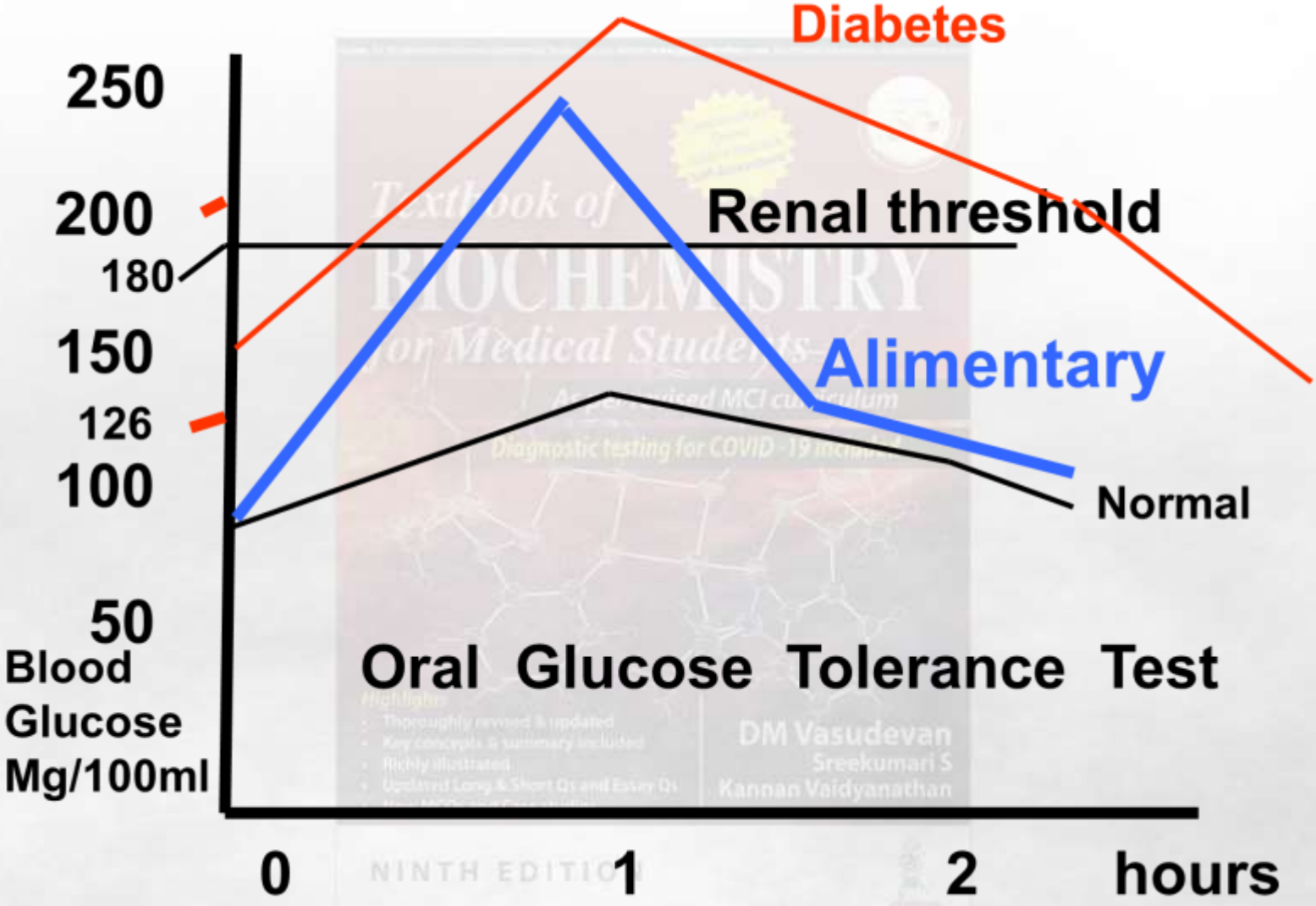
After the child birth, the women should be re-assessed and accordingly classified as having either diabetes mellitus or normal glucose tolerance.

Alimentary Glucosuria

Fasting and 2-hr values are normal.
Exaggerated rise in blood glucose following the ingestion of glucose is seen

One or two urine samples may give a positive Benedict's test.

Increased rate of absorption of glucose from the intestine.
Also seen in hyperthyroidism.


Diabetes
250
200
180
150
126
100
50
Renal threshold
Alimentary
Normal
Blood
Glucose
Mg/100ml
Oral Glucose Tolerance Test
0
1
2
hours

Renal Glucosuria

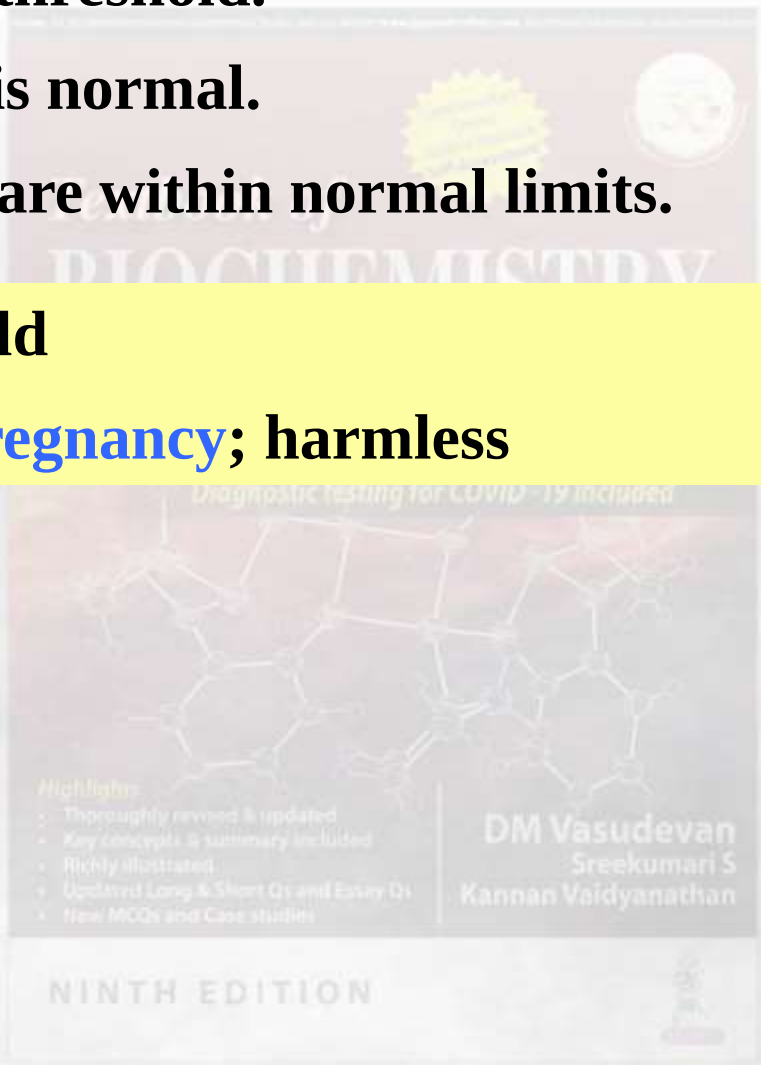
Lowering of renal threshold.

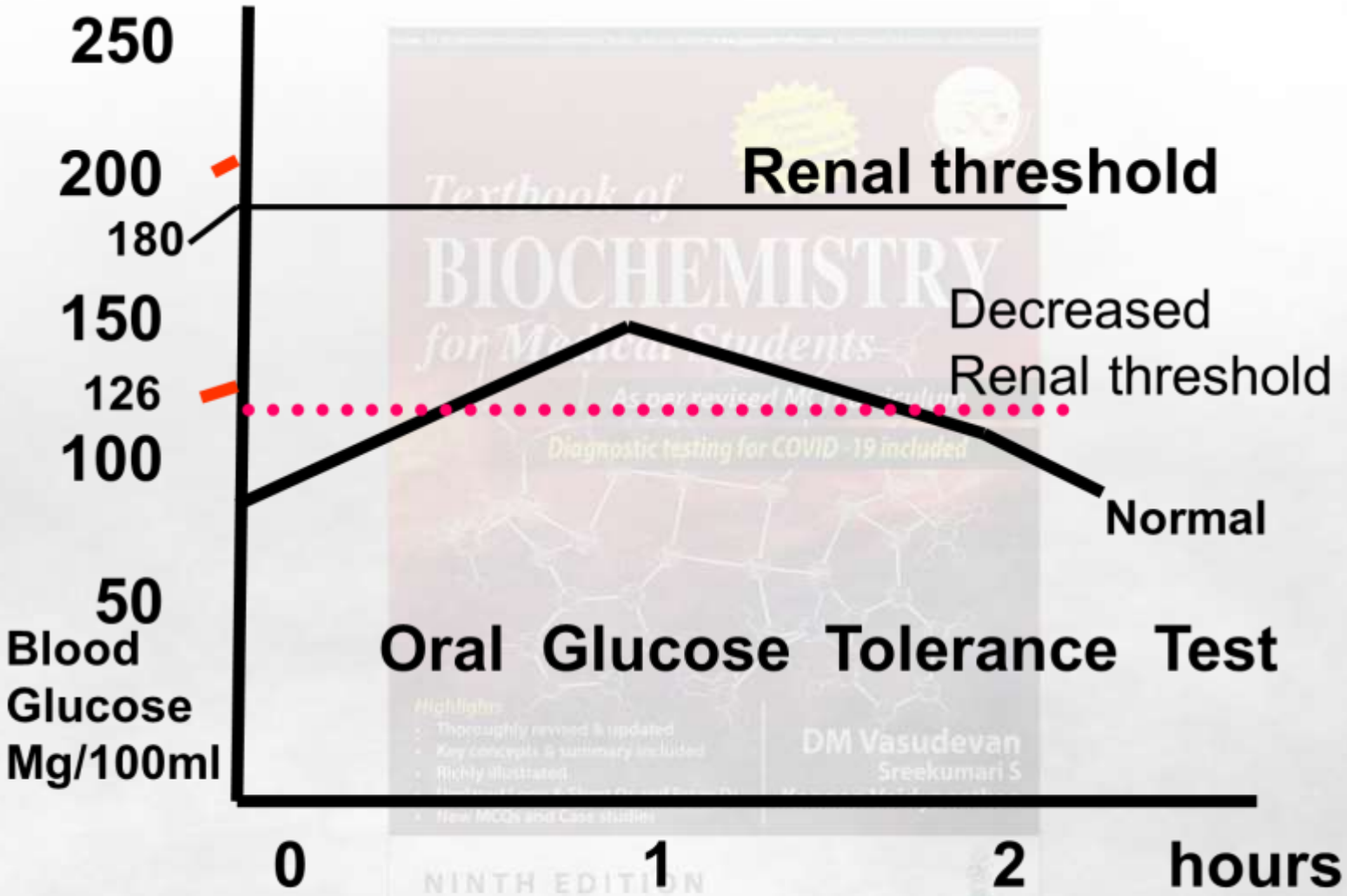
Glucose tolerance is normal.

Blood sugar levels are within normal limits.

Low renal threshold

Physiological in pregnancy; harmless




250
200
180
150
126
100
50
Blood Glucose Mg/100ml
Renal threshold
Decreased Renal threshold
Normal
Oral Glucose Tolerance Test
0
1
2
hours

Reducing Substances in Urine detected by Benedict's test.

Copper Sulphate Sodium Carbonate Sodium Citrate

5 ml Benedict's reagent 0.5 ml of urine boiled for 2 minutes (or kept in a boiling water bath for 2 min).

Semi-quantitative

Colour of precipitate roughly parallels the concentration of reducing sugar.

Blue colour = absence of sugar

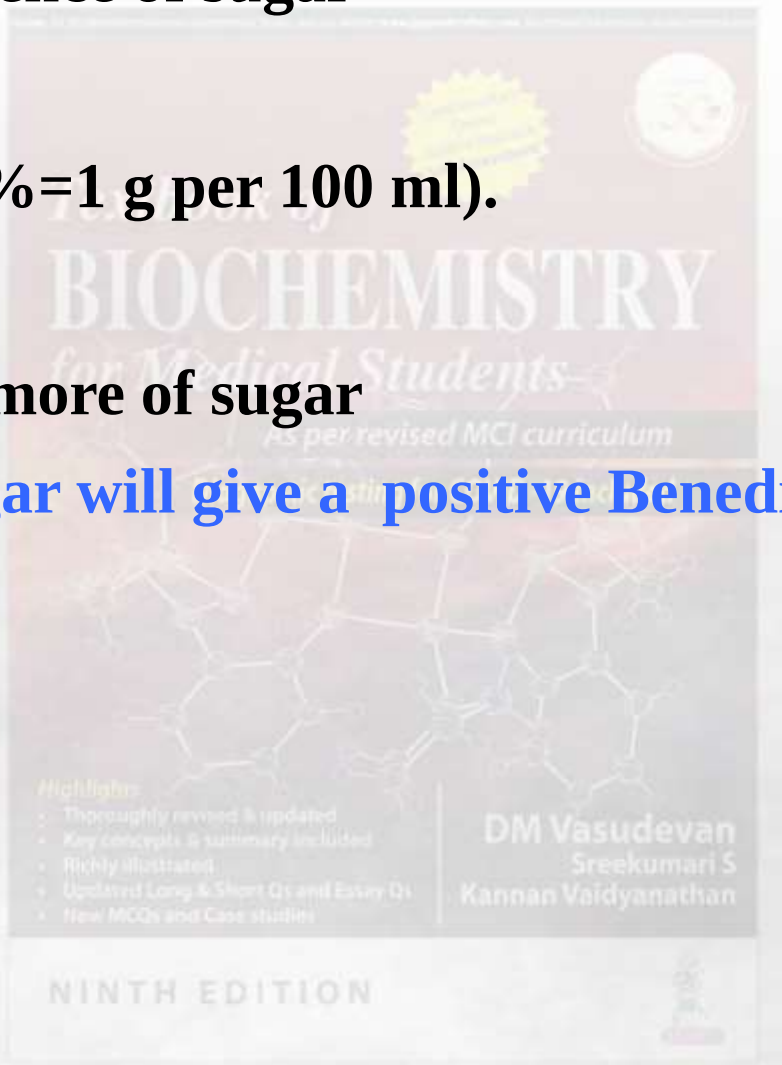
Green = 0.5%

Yellow = 1%; (1%=1 g per 100 ml).

Orange = 1.5%

Red = 2% or more of sugar

Any reducing sugar will give a positive Benedict's test



Reducing Substances in Urine

Sugars

Glucose

Fructose

Lactose

Galactose

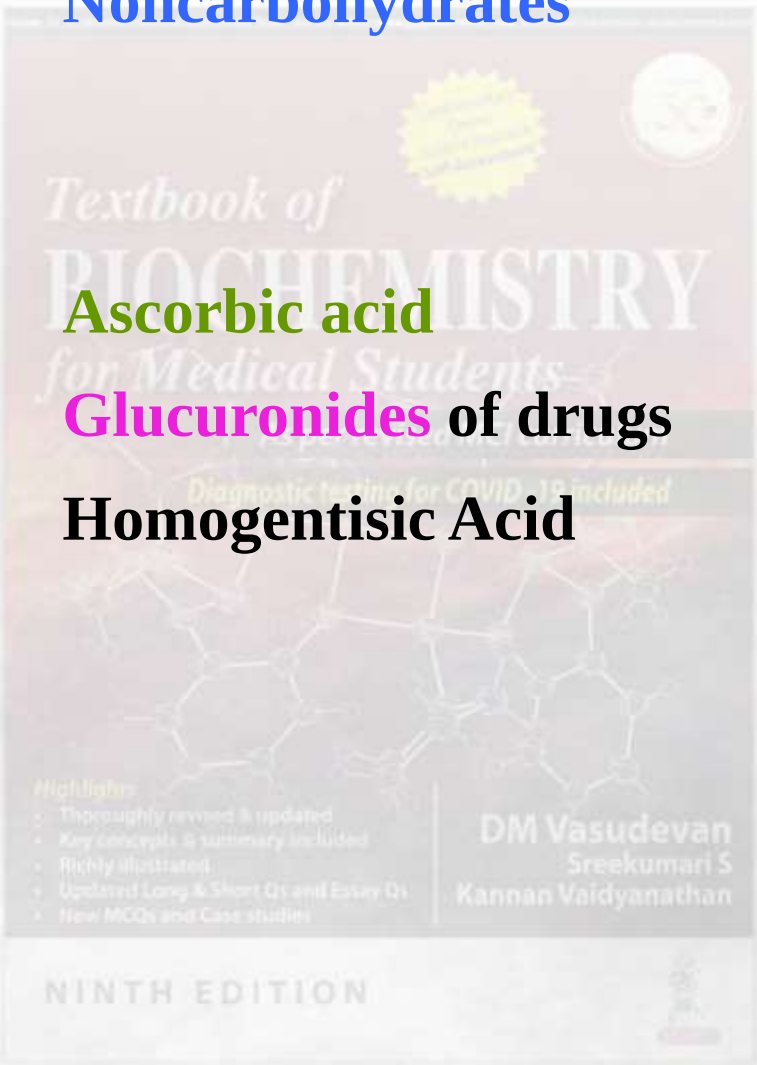
Pentoses

Noncarbohydrates

Ascorbic acid

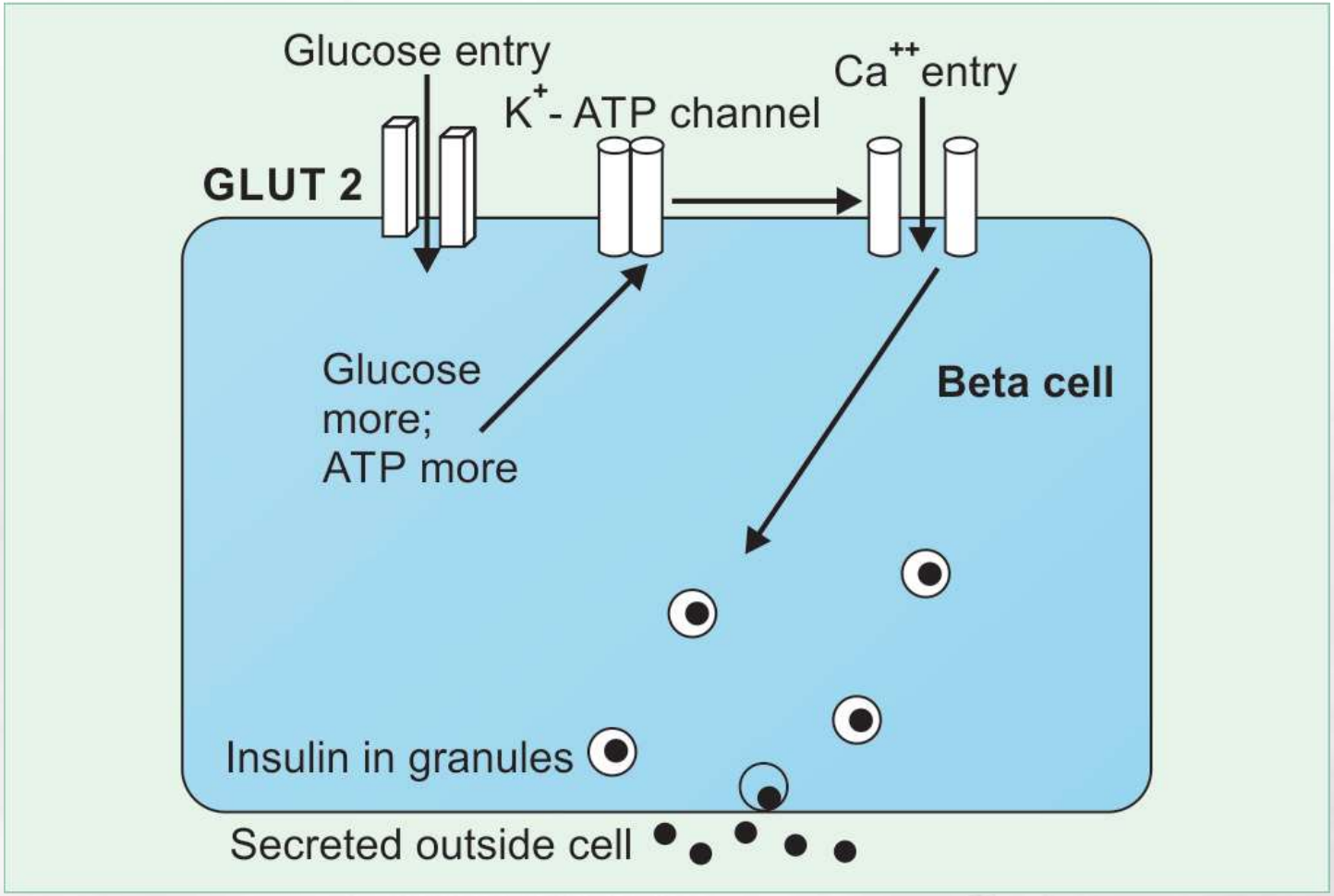
Glucuronides of drugs

Homogentisic Acid

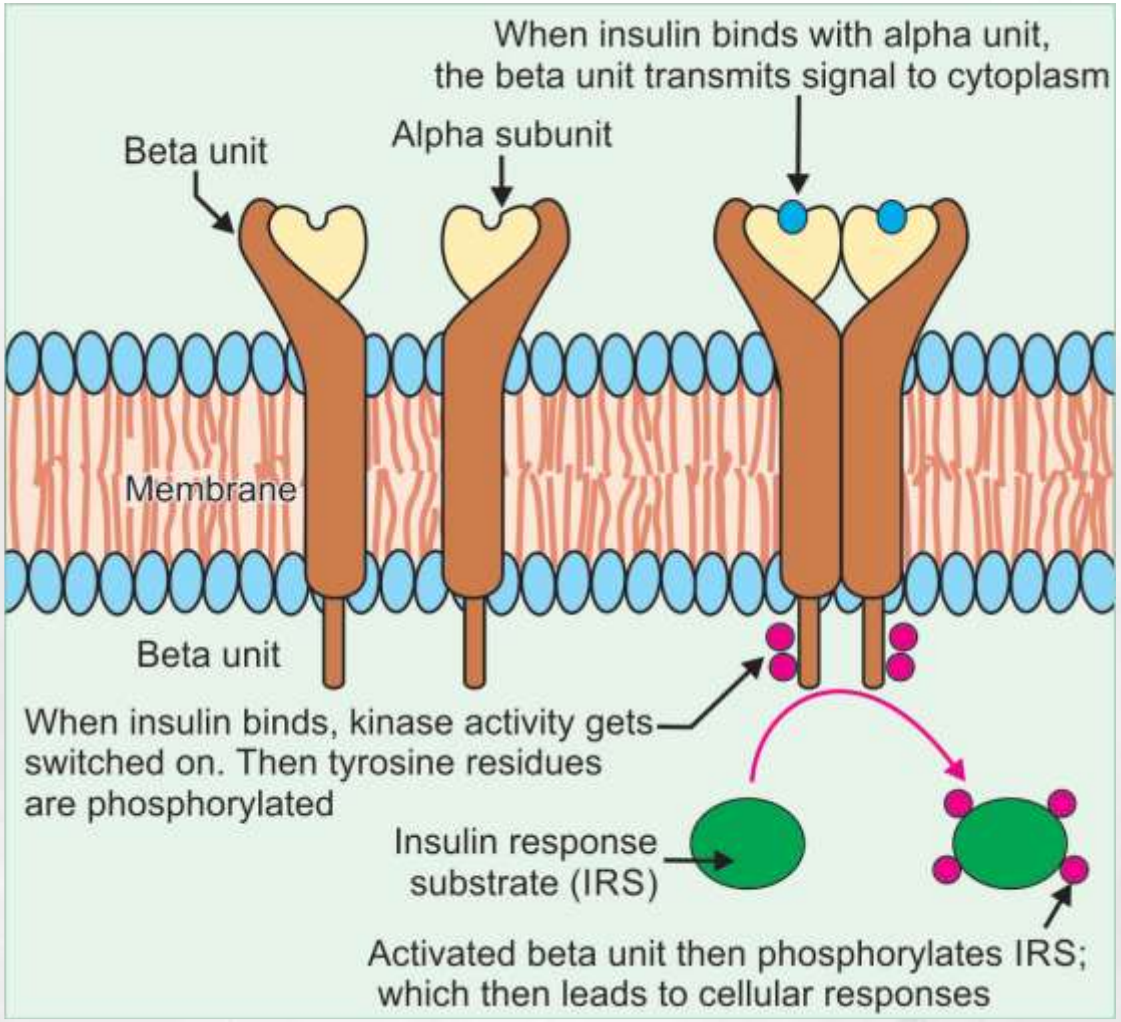


Differential Diagnosis Reducing Substances in Urine

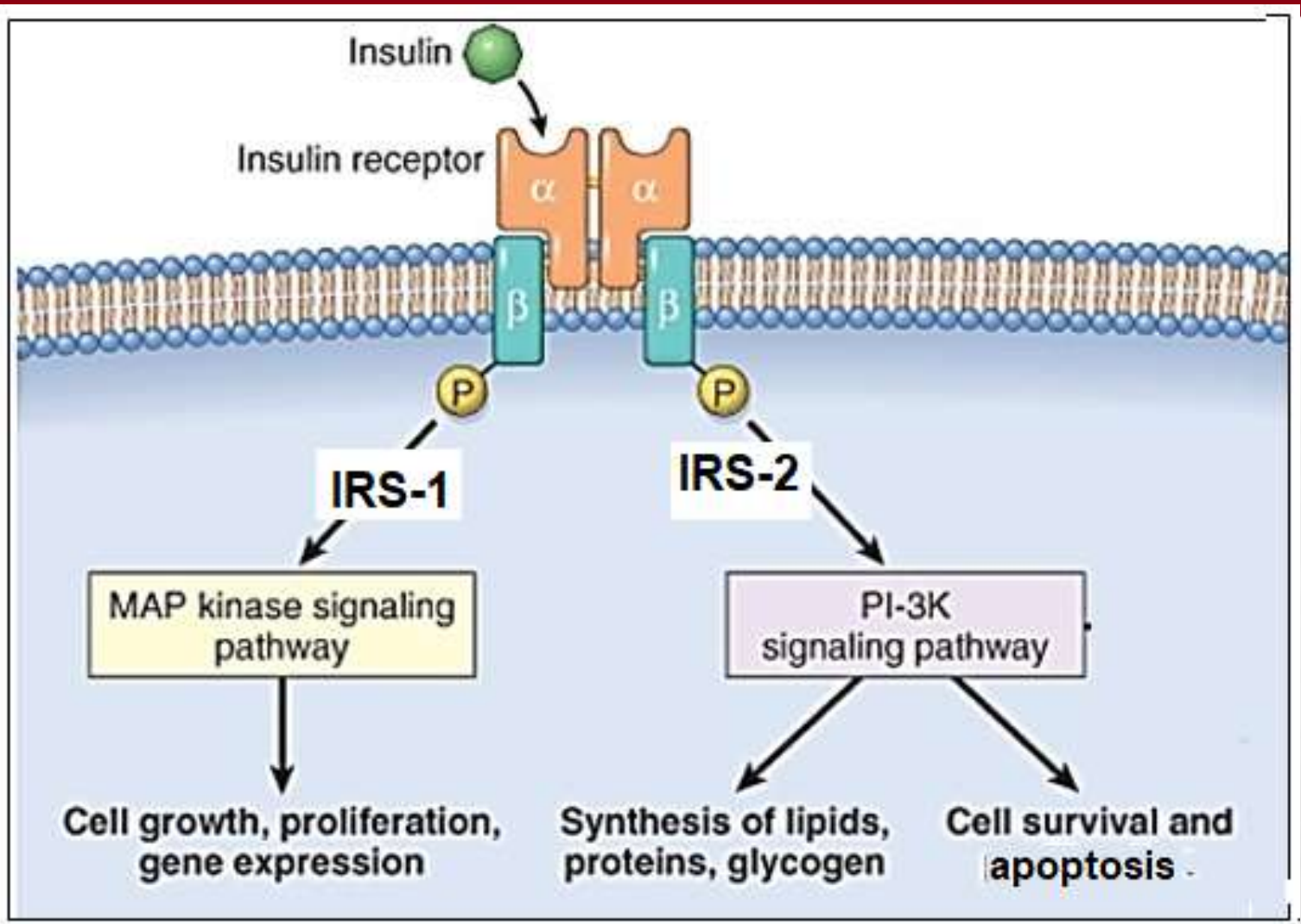
1. Glucosuria
    a. Diabetes mellitus
    b. Transient glycosuria
    c. Alimentary glycosuria
    d. Renal glucosuria
2. Fructosuria
    a. Deficiency of fructokinase
    b. Fructose intolerance (aldolase B deficiency)
3. Lactosuria
4. Galactosuria (deficiency of galactose-1-phosphate uridyltransferase)
5. Pentosuria (Xylulosuria)
6. Noncarbohydrate reducing substances
    a. Glucuronides, salicylate
    b. Ascorbic acid (Vitamin C)
    c. Homogentisic acid



Mechanism of insulin secretion



Insulin receptor.



Insulin signaling. IRS bifurcates the insulin response into different pathways.

Physiological Actions of Insulin

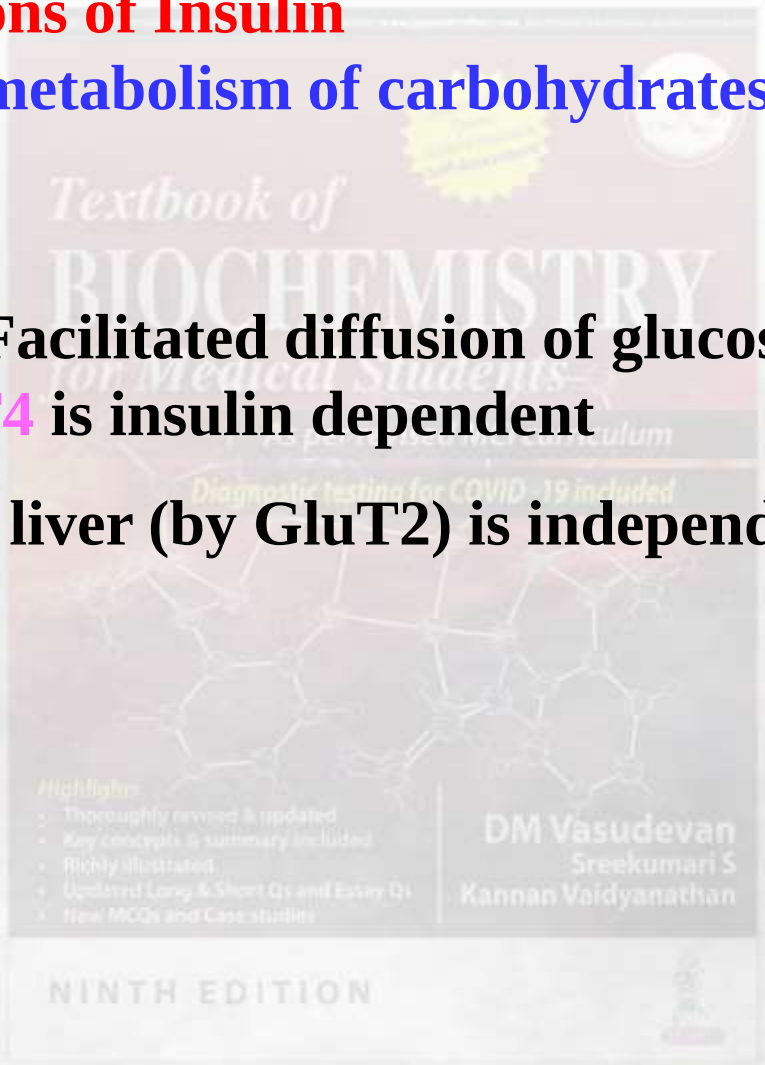
Regulation of the metabolism of carbohydrates, lipids and proteins.

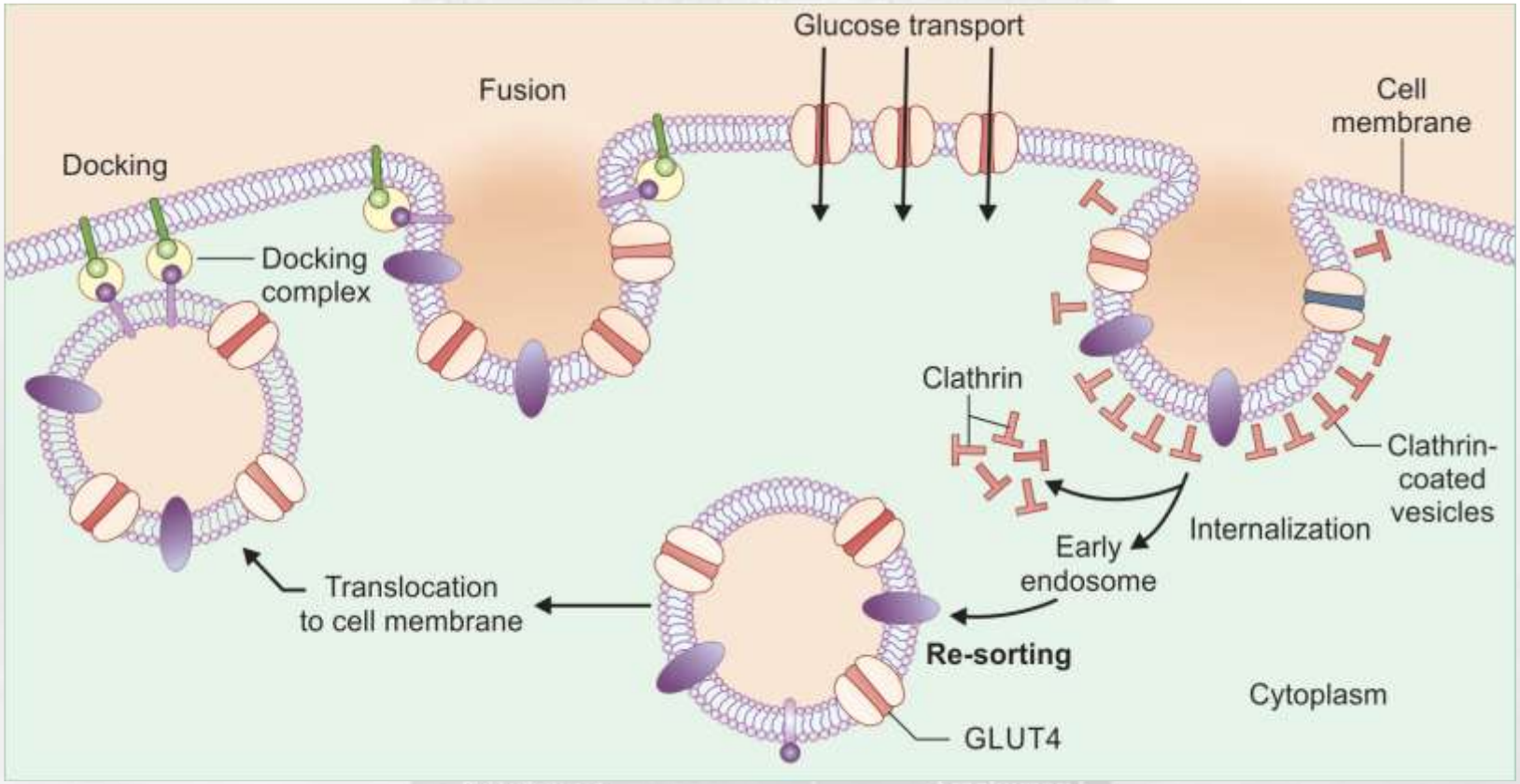
1. Glucose Uptake

Insulin facilitates Facilitated diffusion of glucose in muscle.

Transporter, GIuT4 is insulin dependent

Glucose uptake in liver (by GluT2) is independent of insulin.





Translocation of GLUT4 from intracellular vesicles to the cell membrane, under the influence of the insulin

2. Utilisation of Glucose

Glycolysis increased

key glycolytic enzymes (glucokinase, phosphofructokinase and pyruvate kinase)

3. Insulin favours storage of glucose

Glycogen synthesis increased

Glycogen synthase

4. Lipogenesis increased

Acetyl CoA Carboxylase

Glucose-6-Phosphate dehydrogenase (NADPH)

5. Anti-lipolytic effect

Hormone sensitive lipase

6.Gluconeogenesis Decreased

Key gluconeogenic enzymes

Pyruvate kinase

Phospho enol pyruvate carboxy kinase

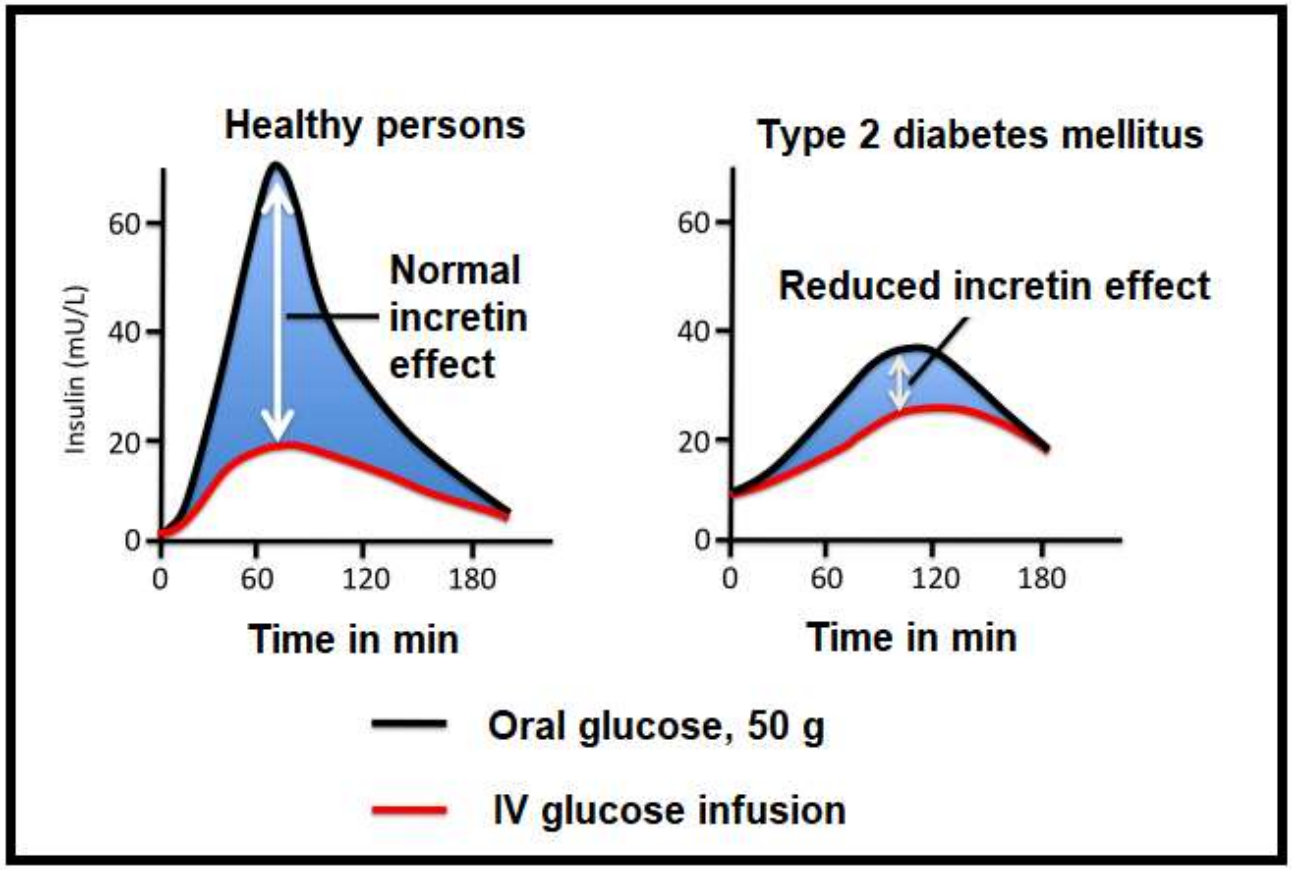
Fructose 1,6 bis phosphatase

Glucose 6 phosphatase

7. Anti-ketogenic Effect

HMG CoA synthase

Incretin Hormones

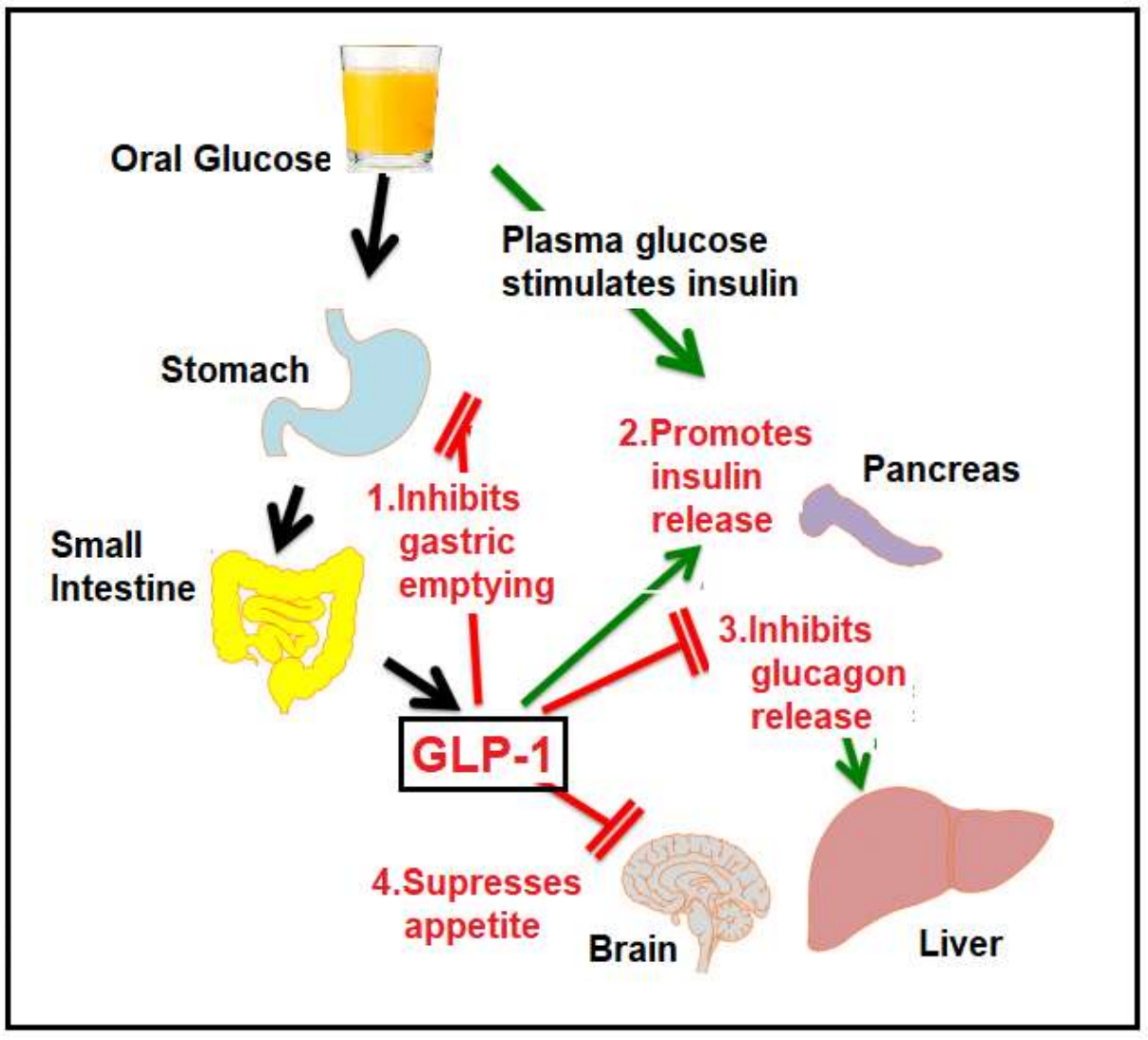


Incretin causes beta cells to secrete *more insulin* in response to the same amount of blood glucose.

Incretin Hormones

- The incretins are hormones that work to increase insulin secretion. Glucose in the small intestine stimulates incretin release. Incretins are carried through the circulation to their target tissue: the pancreatic beta cells. Incretin causes beta cells to secrete more insulin in response to the same amount of blood glucose. Incretin hormones are glucagon-like peptide–1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). **GLP-1** is secreted by the L cells, mainly in the ileum.
- An impaired incretin system, characterized by decreased responsiveness to GLP-1 occurs in individuals with type 2 diabetes mellitus. GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase–4 (DPP-4). DPP-4 inhibitors such as sitagliptin increase endogenous GLP-1 concentration and are useful as oral antidiabetic drugs.

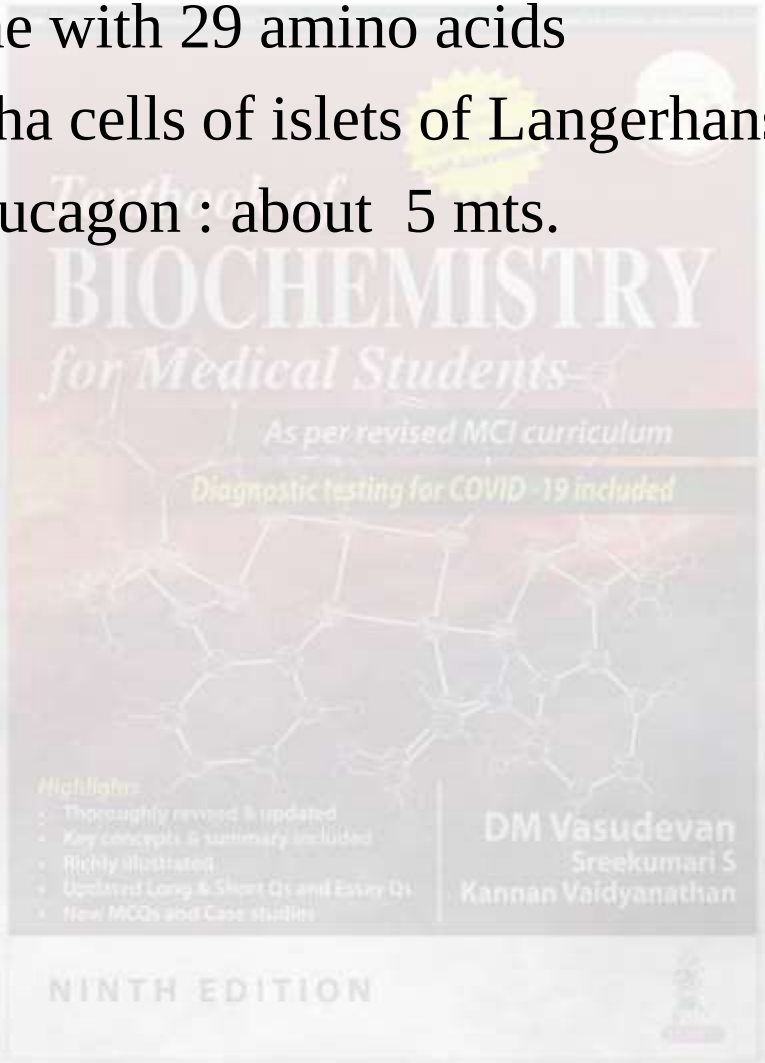
Incretin Hormones



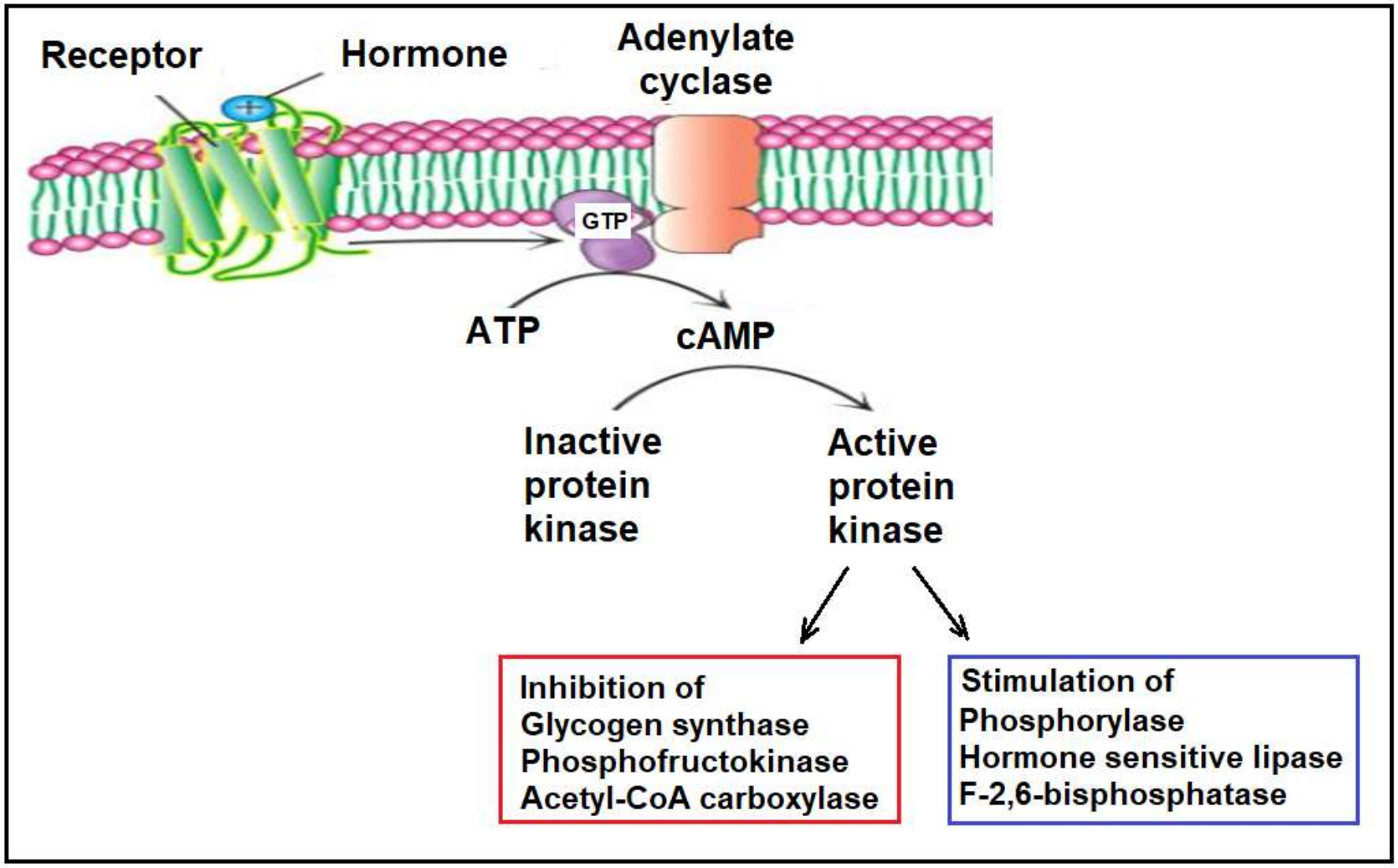
Mechanism of action of GLP-1.

Glucagon.

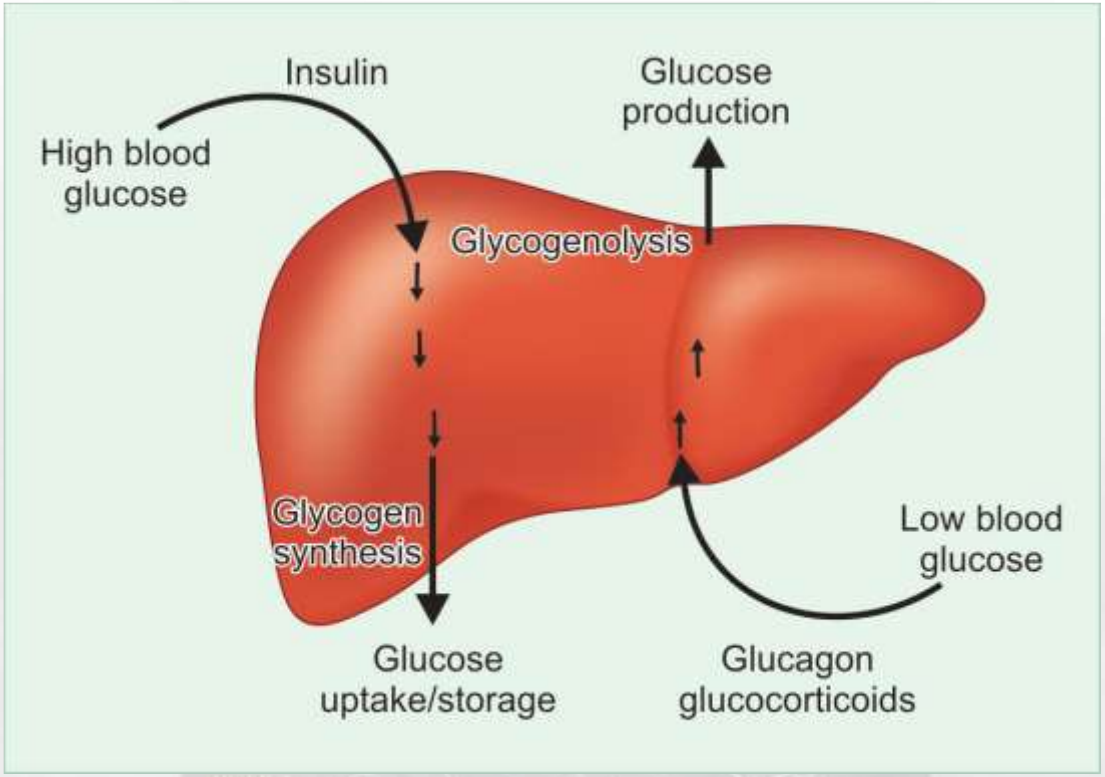
- Peptide hormone with 29 amino acids
- Secreted by alpha cells of islets of Langerhans.
- Half –life of glucagon : about 5 mts.



Mechanism of Action of Glucagon



Metabolism	Insulin	Glucagon
Glycolysis	stimulate	inhibit
Glycogenolysis	inactivate	activate
Gluconeogenesis	inhibit	stimulate
Glycogen synthesis	activate	inhibit
Lipolysis	inhibit	stimulate
Ketogenesis	inhibit	stimulate
Protein	anabolism	catabolism
Blood sugar level	decrease	increase



Combined action of insulin and glucagon will keep the blood glucose level within normal limits. High blood glucose stimulates insulin secretion. Low blood glucose causes glucagon secretion

Biological Effects of Insulin

Meta-bolism	Key enzyme	Action of insulin on the enzyme	Direct effect	Overall effect
Carbo-hydrate	Translocase Glucokinase Phosphofructo kinase Pyruvate kinase	stimulation stimulation stimulation Stimulation	Glycolysis favoured	Hypoglycemia
do	Pyruvate carboxylase PEPCK Fructose-1,6-bisphosphatase Glucose-6-phosphatase	inhibition inhibition inhibition inhibition	Gluconeogenesis depressed	Hypoglycemia
do	Glycogen synthase Glycogen phosphorylase	activation inactivation	Glycogen deposition	Hypoglycemia
do	GPD	stimulation	Generation of NADPH	Lipogenesis

Meta-bolism	Key enzyme	Action of insulin on the enzyme	Direct effect	Overall effect
Lipid	Acetyl-CoA carboxylase Glycerol kinase Hormone sensitive lipase HMG-CoA reductase	stimulation stimulation inhibition stimulation	Lipogenesis Lipogenesis Lipolysis inhibited Cholesterol synthesis	Glucose is used for lipogenesis; glucose lowered
Pro-tein	Transaminases Ornithine transcarbamoylase RNA polymerase	inhibition inhibition favoured	Catabolism inhibited Catabolism inhibited Protein synthesis	General anabolism

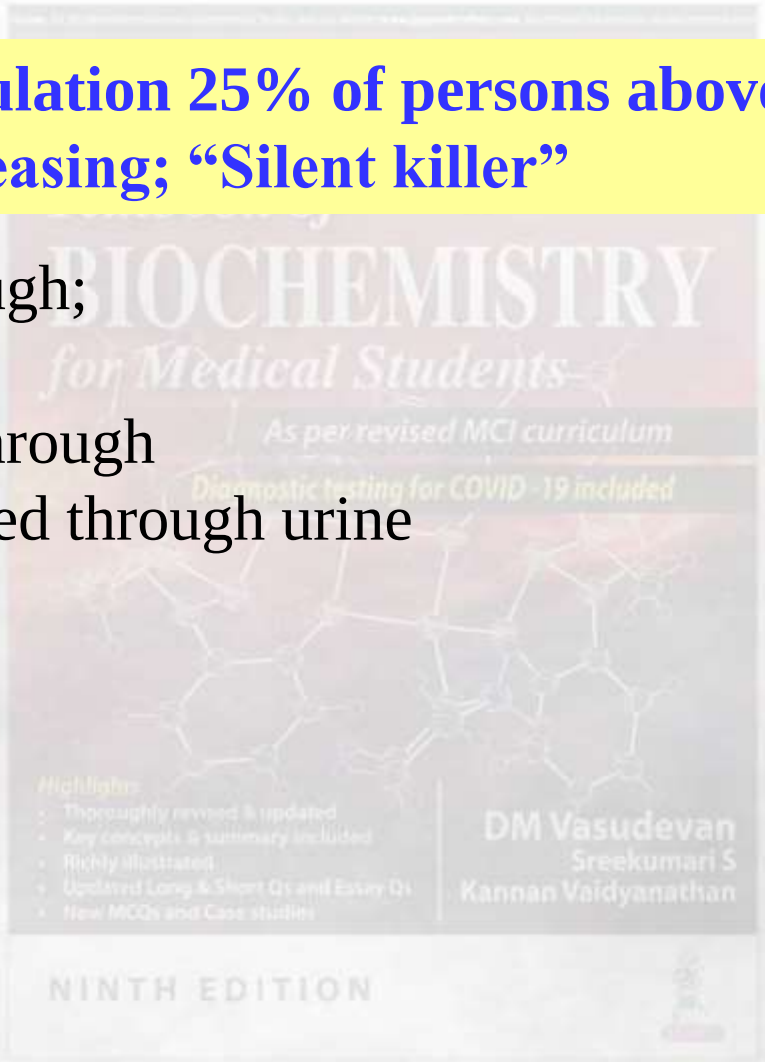
Comparison of Action of Insulin and Anti-Insulin Hormones

Metabolism	Key enzymes	Insulin	Glucagon	Gluco-corticoids	Growth hormone
Glycolysis	GK, PFK and PK	Stimulation			inhibition
Gluconeogenesis	PEPCK, G-6-Pase, F-bisphosphatase	inhibition	Stimulation	Stimulation	Stimulation
Glycogen synthesis	Glycogen synthase	activation	inhibition		
Glycogenolysis	Phosphorylase	Inactivation	activation		
Lipolysis	Hormone sensitive lipase	inhibition	Stimulation	Stimulation	Stimulation
Ketogenesis	Carnitine acyl transferase	Inhibition	Stimulation		Stimulation

Diabetes Mellitus

10% of total population 25% of persons above 50 years
Incidence in increasing; "Silent killer"

Greek, Dia = through;
Bainein = pass
Diabetes = pass through
Body mass is passed through urine
Mellitus = sweet



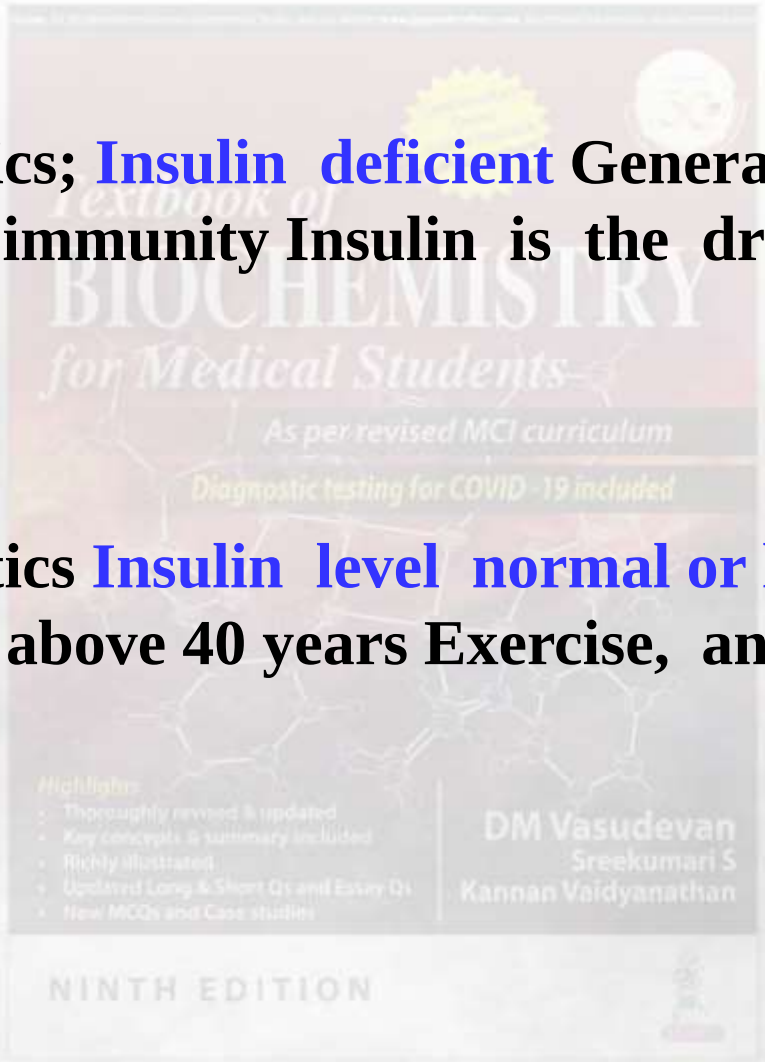
Type 1

5% of all diabetics; Insulin deficient Generally in young; adolescence Auto immunity Insulin is the drug of choice

Type 2

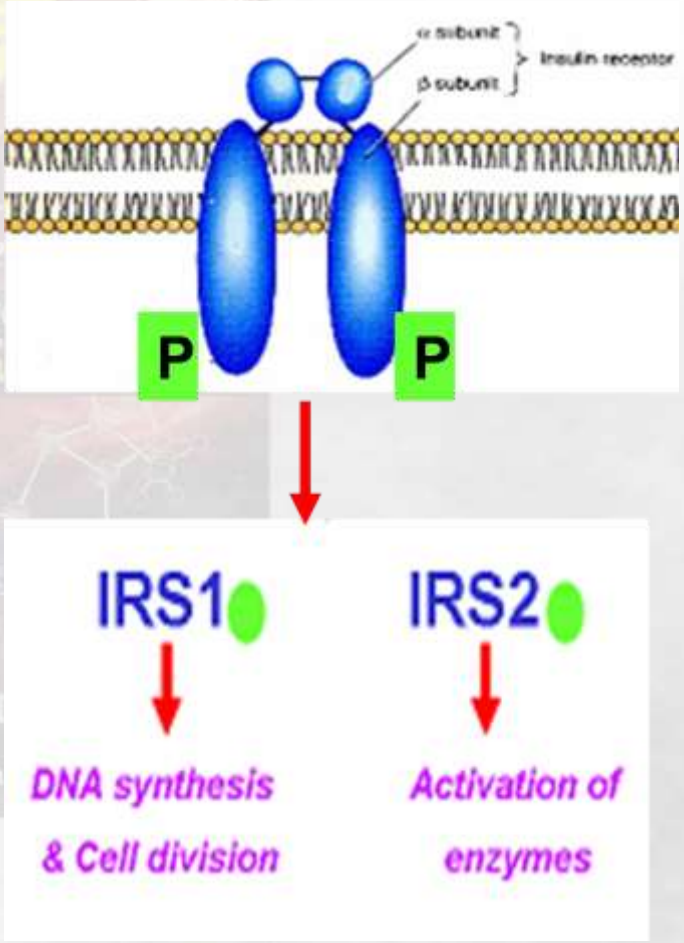
90% of all diabetics Insulin level normal or high

Generally adults, above 40 years Exercise, anti-diabetic drugs

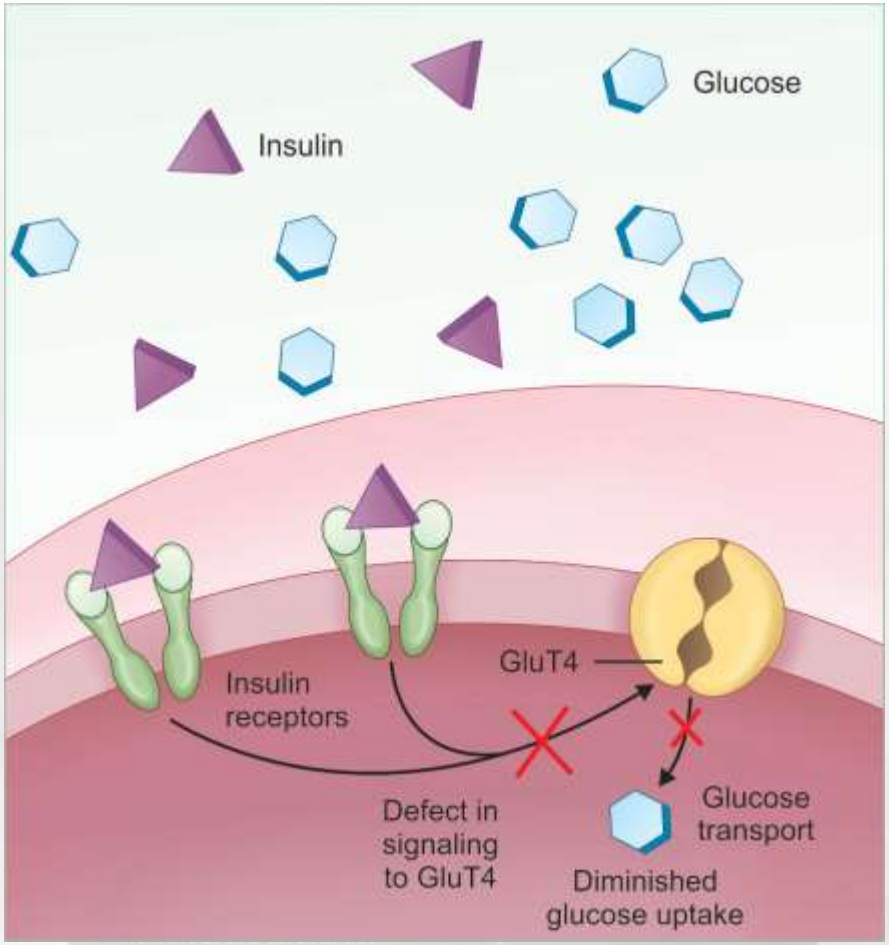


Metabolic Changes in Type 2

- ↓ number of insulin receptors on the peripheral tissues



- Lack of normal response to Insulin



Insulin resistance in diabetes mellitus type 2.
GluT4 receptors are defective in muscle cells.

Plasma Glucose Levels in OGTT in Normal Persons and in Diabetic Patients

	Normal Persons	Criteria for diagnosing diabetes	Criteria for diagnosing IGT
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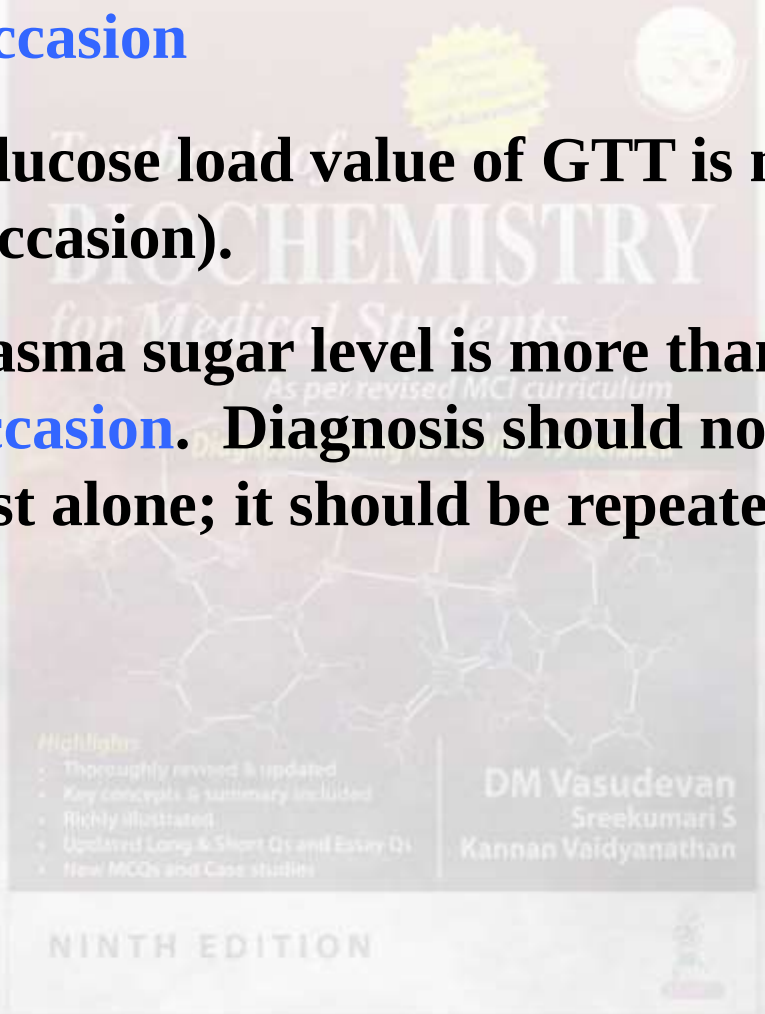
2 hr after Glucose	< 140 mg/dL	> 200 mg/dL	141 to 199 mg/dL

Diagnostic Criteria for Diabetes Mellitus

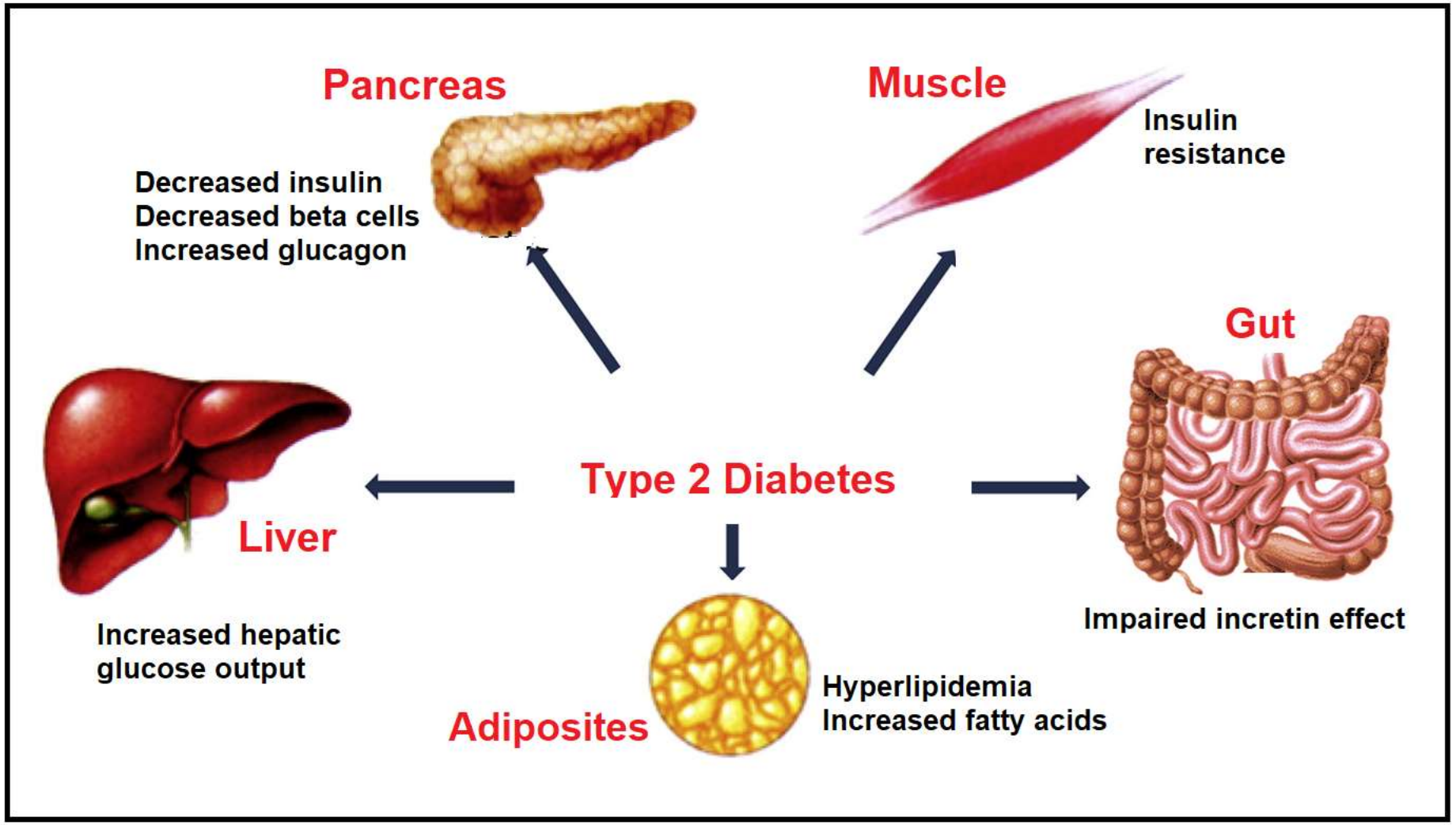
1. If the fasting plasma sugar is more than 126 mg /dl, on more than one occasion
2. Or, if 2-hr post-glucose load value of GTT is more than 200 mg /dl (even at one occasion).
3. If the random plasma sugar level is more than 200 mg/dl, on more than one occasion. Diagnosis should not be based on a single random test alone; it should be repeated.



Criteria for Diagnosis of Metabolic Syndrome

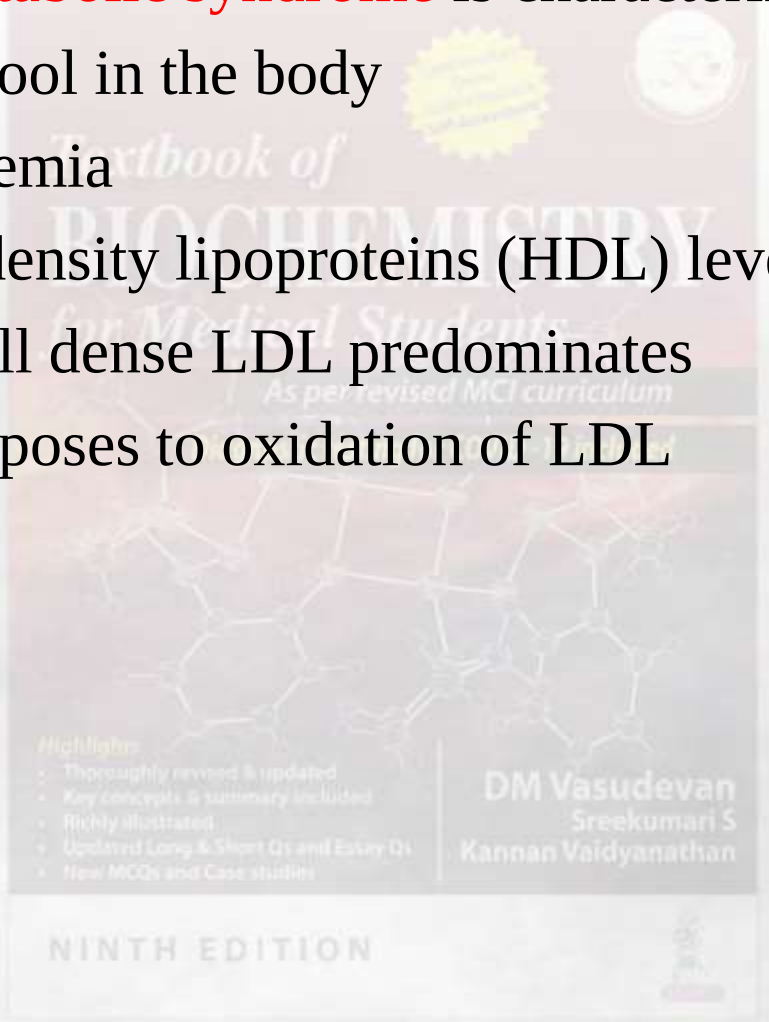
1. Elevated waist circumference: (For men >90 cm and for women, >80 cm)
2. Elevated triglycerides: >150 mg/dL
3. Reduced HDL cholesterol: For men, <40 mg/dL; for women, <50 mg/dL
4. Elevated blood pressure: >130/85 mm Hg
5. Elevated fasting glucose: >100 mg/dL
6. Insulin resistance (hyperinsulinemia)
7. Additional parameters include: coagulation abnormalities, hyperuricemia, microalbuminuria non-alcoholic steatohepatitis (NASH) and increased CRP
8. Diagnosis is made, if any 3 out of the criteria given above.

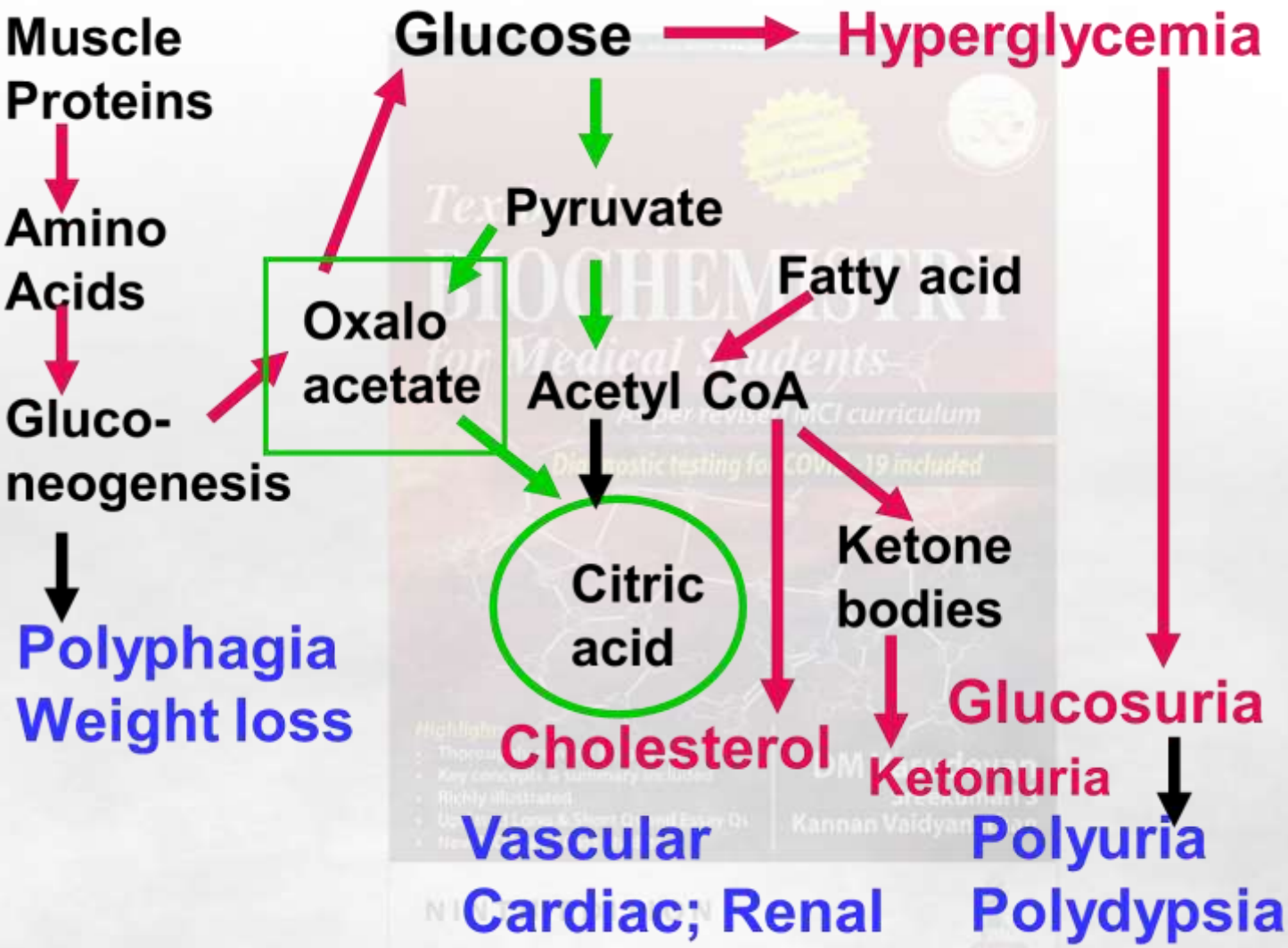
Pathophysiology of Type 2 diabetes mellitus

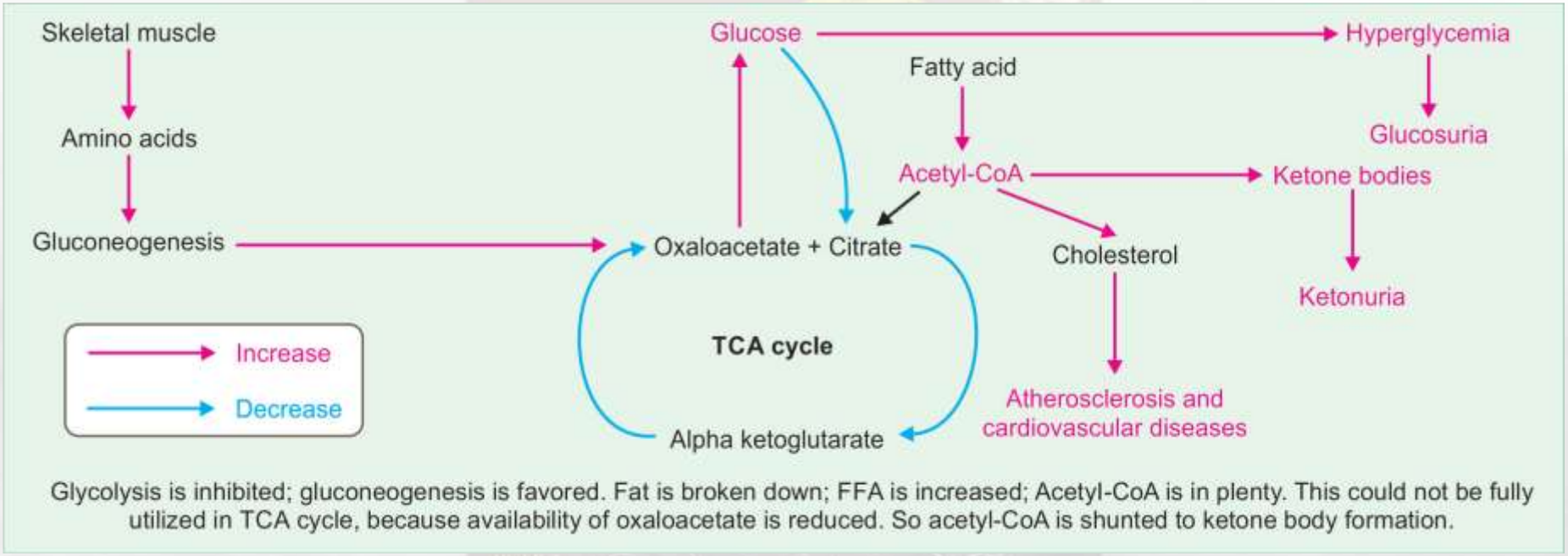


Dyslipidemia in metabolic syndrome is characterized by:

- Increased TAG pool in the body
- Hypertriglyceridemia
- Decreased high density lipoproteins (HDL) level
- Atherogenic small dense LDL predominates
- Low HDL predisposes to oxidation of LDL




Muscle Proteins
Amino Acids
Gluco-neogenesis
Polyphagia
Weight loss
Glucose
Hyperglycemia
Pyruvate
Oxalo acetate
Fatty acid
Acetyl CoA
Citric acid
Ketone bodies
Cholesterol
Ketonuria
Glucosuria
Vascular
Cardiac; Renal
Polyuria
Polydypsia



Glycolysis is inhibited; gluconeogenesis is favored. Fat is broken down; FFA is increased; Acetyl-CoA is in plenty. This could not be fully utilized in TCA cycle, because availability of oxaloacetate is reduced. So acetyl-CoA is shunted to ketone body formation.

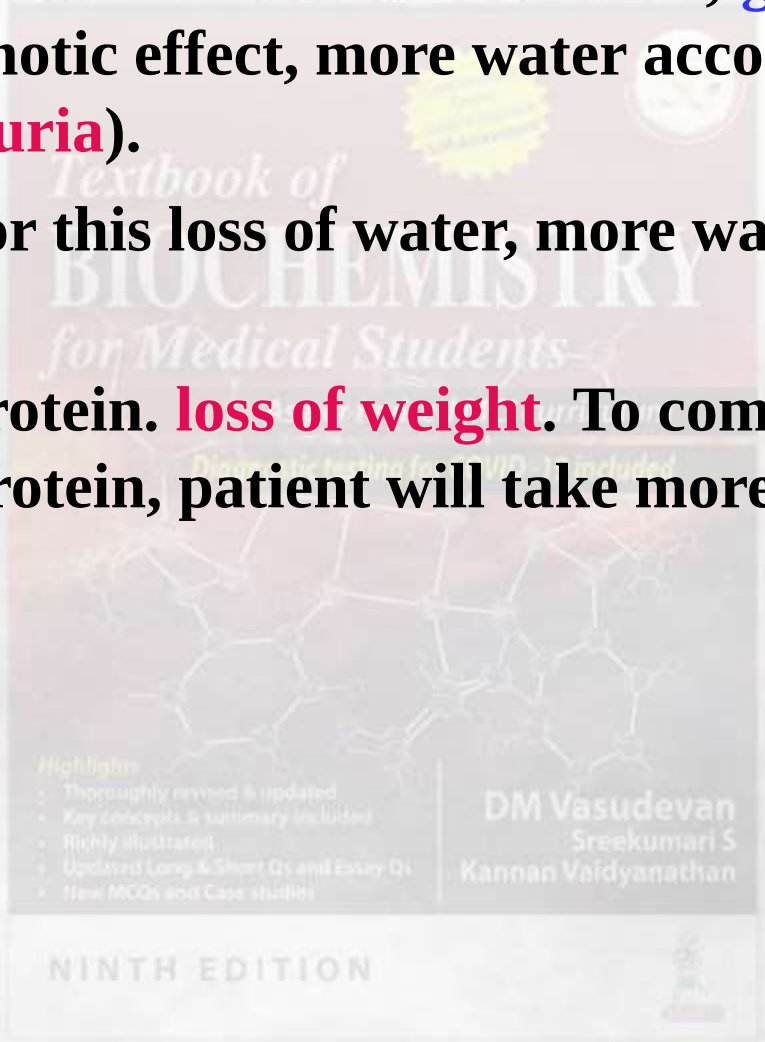
Metabolic derangements in diabetes mellitus

Cardinal Symptoms

Blood glucose level exceeds renal threshold; glucose in urine. Due to osmotic effect, more water accompanies the glucose (polyuria).

To compensate for this loss of water, more water is taken (polydypsia).

Breakdown of protein. loss of weight. To compensate the loss of glucose and protein, patient will take more food (polyphagia).



Immediate Complications

Infections

Ketosis, ketonuria

Hypercholesterolemia

Hypertension

Chronic complications

Myocardial infarction

Micro angiopathy

Diabetic retionopathy; Cataract

Diabetic renopathy; renal failure

Neuropathy; Diabetic gangrene

Diabetic Ketoacidosis

Ketosis is more common in type 1 diabetes mellitus.
When the rate of synthesis exceeds the ability of extrahepatic tissues to utilize them,
there will be accumulation of ketone bodies in blood.

This leads to **ketonemia**, excretion in urine (**ketonuria**) and smell of **acetone** in breath. All these three together constitute the condition known as **ketosis**.

Diagnosis of Ketosis

Detection of ketone bodies in urine by **Rothera's test**. Supportive evidence may be derived from estimation of serum electrolytes, acid-base parameters and glucose estimation.

Causes for Ketosis

- **Diabetes mellitus:**

The combination of hyperglycemia, glucosuria, ketonuria and ketonemia is called **diabetic ketoacidosis** (DKA). Untreated diabetes mellitus is the most common cause for ketosis.

- **Starvation:**

In starvation, the dietary supply of glucose is decreased. Available oxaloacetate is channeled to gluconeogenesis. The increased rate of lipolysis provides excess acetyl-CoA which is channeled to ketone bodies. The high **glucagon** favors ketogenesis.

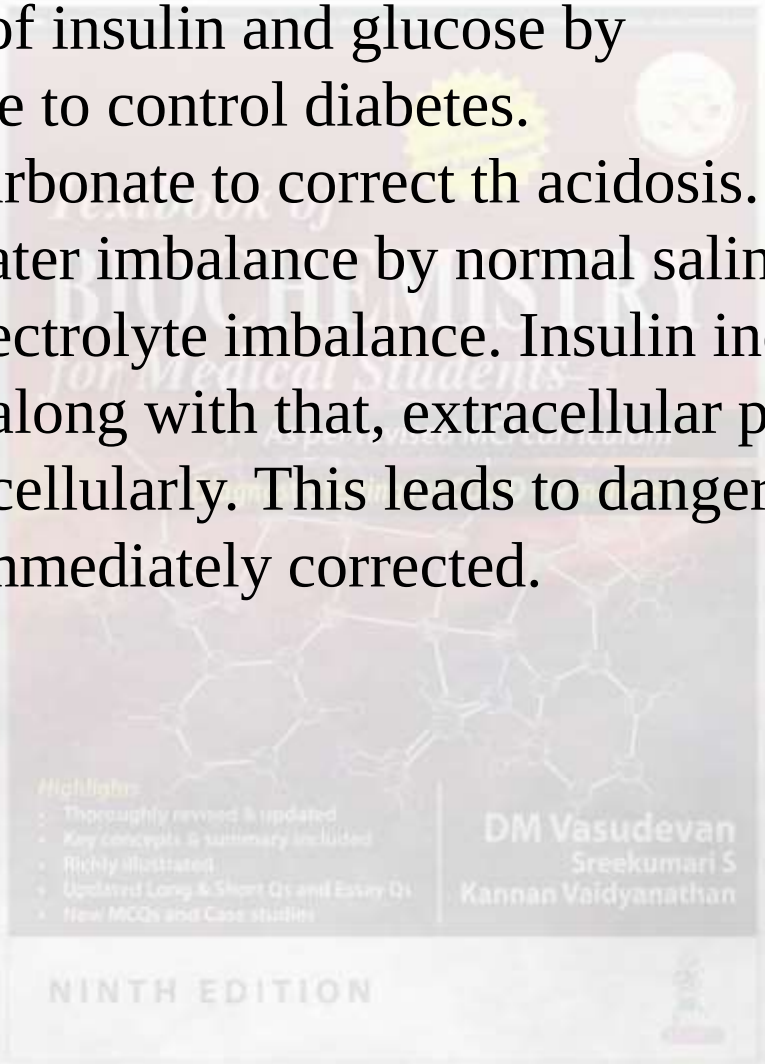
In both diabetes mellitus and starvation, the oxaloacetate is channeled to gluconeogenesis; so, the availability of oxaloacetate is decreased. Hence, acetyl-CoA cannot be fully oxidized in the TCA cycle.

Consequences of Ketosis

- **Metabolic acidosis:** Acetoacetate and beta-hydroxy butyrate are acids. There will be an increased **anion gap.**
- **Reduced buffers in blood**
- **Kussmaul's respiration:** due to compensatory hyperventilation.
- **Smell of acetone** in patient's breath.
- **Osmotic diuresis** induced by ketonuria may lead to dehydration.
- **Sodium loss:**
- **High potassium:** Due to lowered uptake of potassium by cells in the absence of insulin.
- **Dehydration:** The sodium loss further aggravates the dehydration.
- **Coma:** Hypokalemia, dehydration and acidosis contribute to the lethal effect of ketosis.

Management of Ketosis

- Administration of insulin and glucose by intravenous route to control diabetes.
- Intravenous bicarbonate to correct th acidosis.
- Correction of water imbalance by normal saline.
- Correction of electrolyte imbalance. Insulin induces glycogen deposition, and along with that, extracellular potassium is distributed intracellularly. This leads to dangerous hypokalemia, which is to be immediately corrected.



Hyperosmolar Nonketotic Coma

It can result due to elevation of glucose to very high levels (900 mg/dL or more).

This would increase the osmolality of extracellular fluid (ECF).

Osmotic diuresis leads to water and electrolyte depletion.

The coma results from dehydration of cerebral cells due to hypertonicity of ECF.

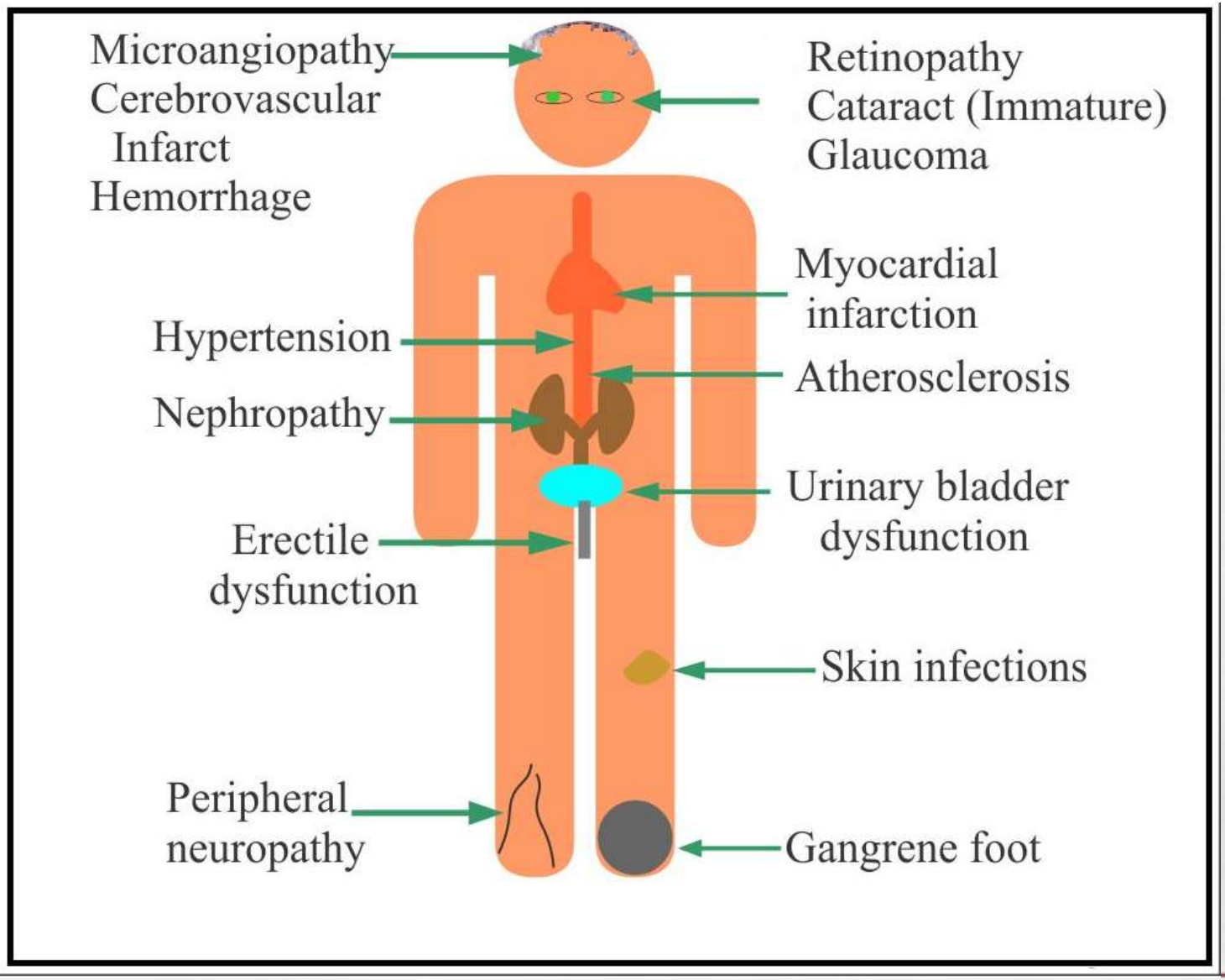
Lactic Acidosis

It occurs due to overproduction and or underutilization of lactic acid. Overproduction can result from an increased rate of anerobic glycolysis due to hypoxia. Underutilization may be due to impairment of TCA cycle.

It was common when diabetes was treated with biguanides in earlier days. The biguanides inhibits mitochondrial oxidative phosphorylation and gluconeogenesis. Newer preparations like Metformin do not have this effect.

Another important cause for lactic acidosis is excess intake of alcohol.

Chronic complications of diabetes mellitus



Glycated Hemoglobin

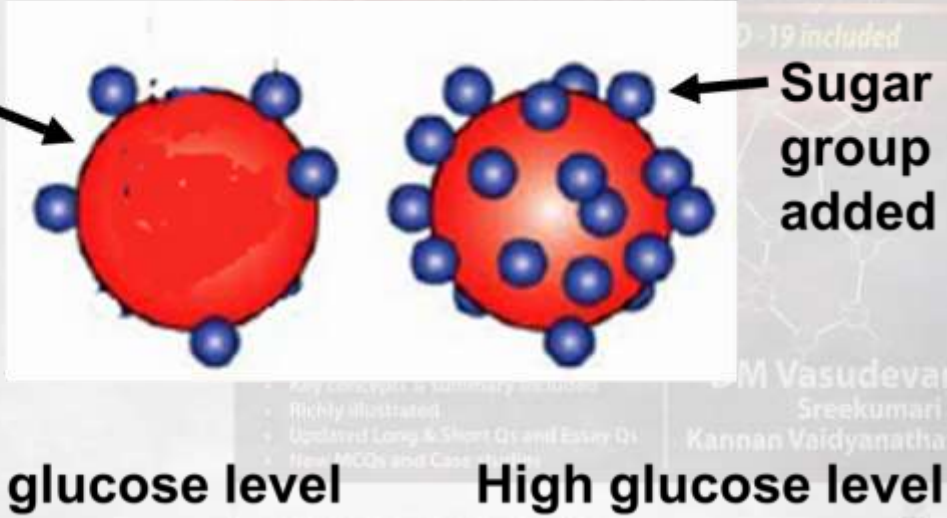
Glycation = non-enzymatic

Glycosylation = enzymatic; purposeful

Glucose + Hb → glyco-Hb

Hb A1c

N-terminal valine of beta chain of Hemoglobin



Glycation is parallel to blood glucose level

Glyco Hemoglobin

Not for diagnosis Important for monitoring
Normal level of HbA1c is < 6 %

Average glucose concentration During the last 120 days.

The best index of long term control of blood glucose level is measurement of glycated hemoglobin or glyco-hemoglobin.

Interpretation of Glyco-Hb Values

Normal level of Hb A1c	: <5.5%
Impaired glucose tolerance	: 5.6-6.5%
Well controlled diabetes	: 6.6-7 %
Partially controlled diabetes	: 7-8%
Uncontrolled diabetes	: 8–10%.

Reduction in 1% of glycoHb will decrease long term complications to an extent of 30%.

The estimation should be done atleast every 3 months in all patients on treatment.

Better once in two months

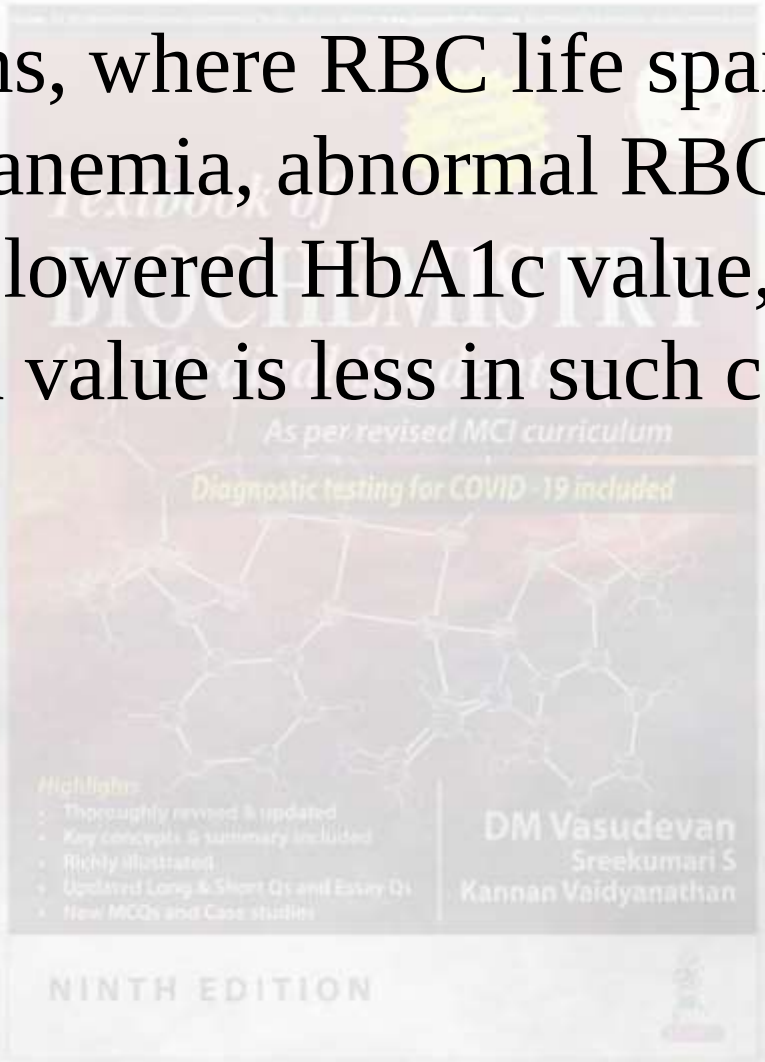
Advantages of HbA1c over fasting plasma glucose estimation

- For HbA1c, fasting sample is not required; the test may be done at any time.
- Low intraindividual variability, less than 2%.
- HbA1c sample is stable; while blood glucose level is lowered unless precautions are taken.

- HbA1c value is not altered by acute factors, while many factors will affect plasma glucose values.
- HbA1c reflects long-term glucose control, while plasma glucose estimation will show the result of a particular point of time only.
- HbA1c is a better index for predicting complications, such as retinopathy.
- HbA1c is unaffected by recent food intake or recent changes in blood glucose.

Precautions for Interpretations

Any conditions, where RBC life span is reduced (e.g. anemia, abnormal RBCs, pregnancy) will reflect in lowered HbA1c value, because the time averaged value is less in such conditions.



Fructosamines and Glycated Albumin

Albumin is also glycated in diabetes mellitus. Glycated albumin is more correctly called as **fructosamino albumin**.

As half-life of albumin is about 20 days, glycated-albumin concentration reflects the glucose control over a recent past, for a period of last 2–3 weeks.

Estimation of fructosamine albumin (glycated albumin) is preferred in the following conditions:

- Change in diabetes treatment, to assess the effectiveness of the medicines given in the recent past.
- Pregnancy, gestational diabetes mellitus, hemolytic anemias of any cause, and hemoglobinopathies. In these conditions, the RBC lifespan is reduced, and so estimation of HbA1c is not valid.

Advanced Glycation End Products (AGEs or AGEP)

Glycation of matrix proteins is completely irreversible. Glycation of collagen alters the properties; cross linking is increased and **elasticity** of collagen is lost. The **advanced glycation end products** (AGE) deposition in tissues and endothelium leads to all the chronic complications of diabetes mellitus. In diabetes, there will be protein adduct formation and consequent protein inactivation. Histones in the nucleus are rich in lysine, and therefore forms the glycated protein N6-carboxymethyl-lysine.

Adhesion of plasma proteins in the altered blood vessels leads to accumulation of LDL, and consequent **atherosclerosis**. Oxidized LDL is the starting factor in the development of atherosclerosis.

Treatment

Diet

Weight reduction to ideal body wt Avoid sugar and sweets

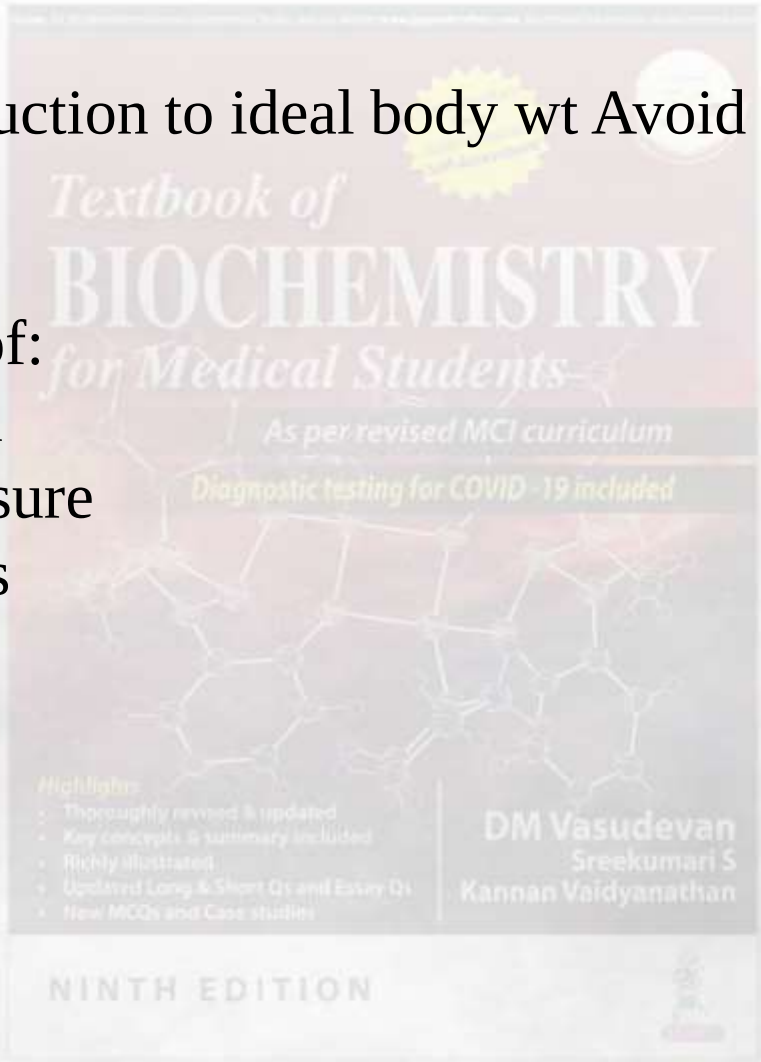
Exercise

Adequate control of:

Cholesterol

Blood pressure

Anti-diabetic drugs



Management of Diabetes Mellitus

Diet and Exercise

This is the first line of treatment.

Oral Hypoglycemic Agents

- The sulfonylureas (e.g. Tolbutamide and Glibenclamide) will stimulate insulin secretion.
- Since they may cause alarming hypoglycemia, biguanides (e.g. Metformin) are more preferred.
- Glitazones or gliptins are dipeptidyl peptidase inhibitors, that inhibit the breakdown of GLP1 and increase the incretin effect.
- Alpha glucosidase inhibitor, **acarbose** inhibits the alpha glucosidases. So, absorption of glucose is reduced.

Management of Diabetes Mellitus

Insulin Replacement Therapy

Insulin is the drug of choice in type 1 disease. It is also used in type 2 disease, where oral drugs are not sufficient.

- **Rapid-acting insulin:** Rapid acting insulin analogs (Insulin Aspart, Insulin Lispro) have an onset of action of 5–15 minutes, peak effect in 1 to 2 hours and duration of action that lasts 4–6 hours.
- **Short-acting insulin:** Regular human insulin (humulin, prepared by recombinant technology) has peak effect in 2 to 4 hours, and duration of action of 6 to 8 hours.
- **Long-acting insulin:** Long-acting insulin analogs (Insulin Glargine) have action that lasts 12–24 hours. During insulin therapy, patient should be closely watched, as overdose may lead to hypoglycemia.

Somogyi Effect and Dawn Phenomena

Somogyi effect is also called Somogyi rebound or posthypoglycemic hyperglycemia. It is a rebound high blood glucose, as a response to low blood glucose. During insulin therapy, especially with long-acting insulins, there is over-abundance of insulin at night, leading to hypoglycemia at 3 am, resulting in high blood glucose at 6 am. When the blood glucose level falls below normal, the body responds by releasing the glucagon, incretins, epinephrine, corticosteroids and growth hormone.

Somogyi Effect and Dawn Phenomena

The **dawn phenomenon** is a morning rise in blood glucose in response to waning insulin and a growth hormone surge that further antagonizes insulin. The high morning blood glucose data is misjudged due to insufficient night time insulin delivery. So, more insulin may be given, leading to further hypoglycemia, and worsening of the situation. Therefore, identification of this hypoglycemia is of paramount importance in treating diabetes.

Hypoglycemia

Hyperglycemia is harmful; but hypoglycemia is **fatal**.
A fall in plasma glucose <50 mg/dL is life-threatening.

Causes of hypoglycemia:

- **Overdose of insulin**: This is the most common cause.
- **Postprandial hypoglycemia:** 2–3 hours after a meal, transient hypoglycemia is seen in some persons. This is due to oversecretion of insulin.
- **Insulinoma:** Insulin secreting tumors

Laboratory Tests in Proven Diabetics

Blood glucose monthly

Lipid profile once in a year

Cholesterol, LDL, HDL, Triglycerides

Micro albuminuria once in a year

Serum creatinine once in a year

Glycated Hb monthly