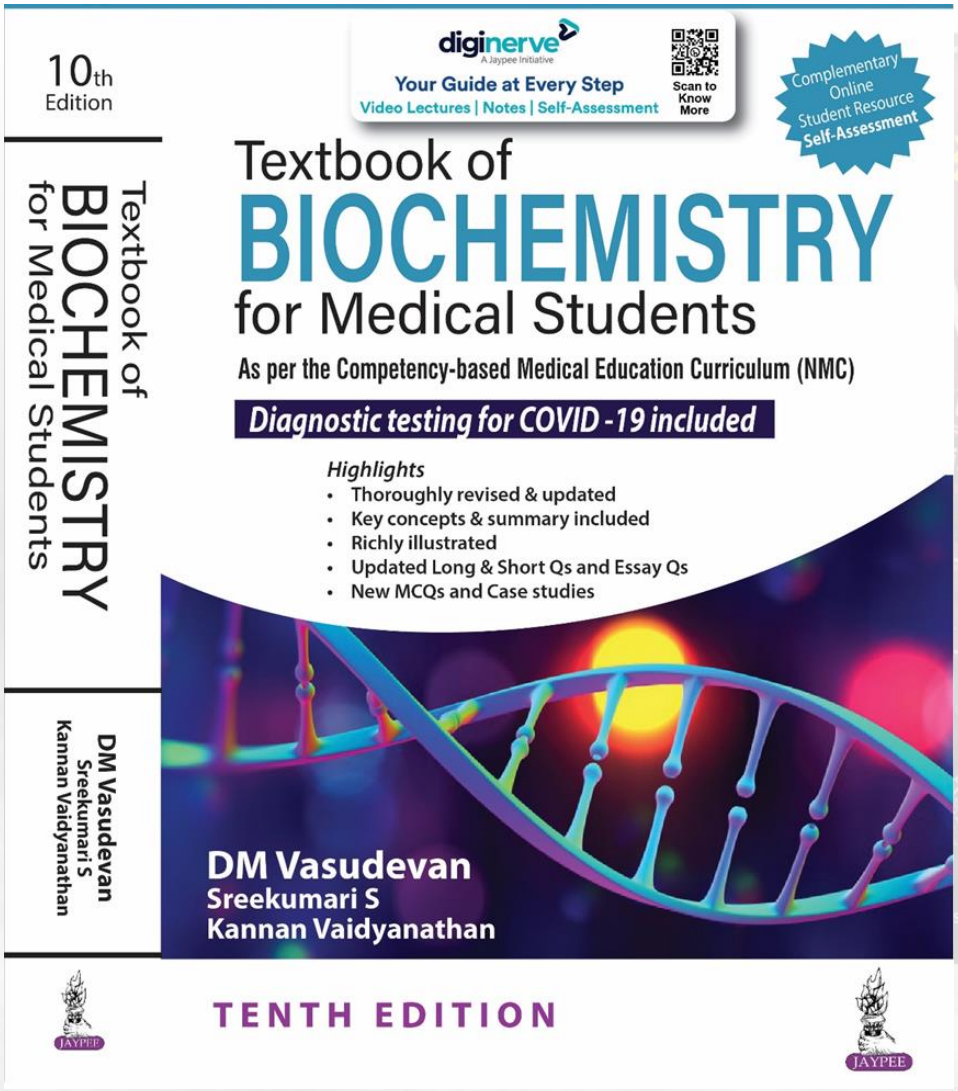


Chapter 18:

Inborn Errors of Metabolism, Prenatal Screening, and Newborn Screening

Textbook of
BIOCHEMISTRY
for Medical Students

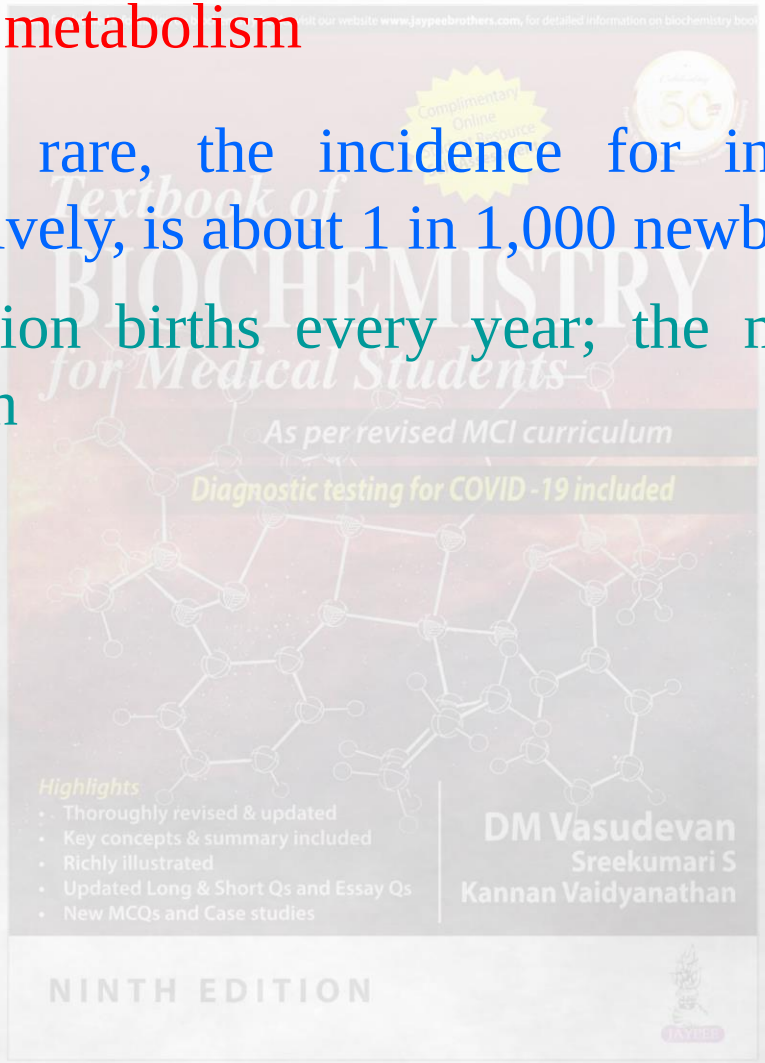
By DM Vasudevan, *et al.*

TENTH EDITION

500 inborn errors of metabolism

While individually rare, the incidence for inborn errors of metabolism, collectively, is about 1 in 1,000 newborns

India with 28 million births every year; the magnitude of the problem is very high



OMIM Database

The discovery of several different types of disorders necessitated the need for an authentic and comprehensive database available to identify and confirm genetic disorders detected in patients. As a result, the Online Mendelian Inheritance in Man (OMIM) database was set up. It is a database that has assigned a specific OMIM number to the phenotype and another ID for the genotype. It provides all necessary information regarding clinical features, genetic and chromosomal locus, and phenotype and genotype identification. By matching disease manifestations and other phenotypic features, the particular genetic defect in a patient can be correctly identified.

Undetected cases of metabolic disorders lead to permanent mental retardation

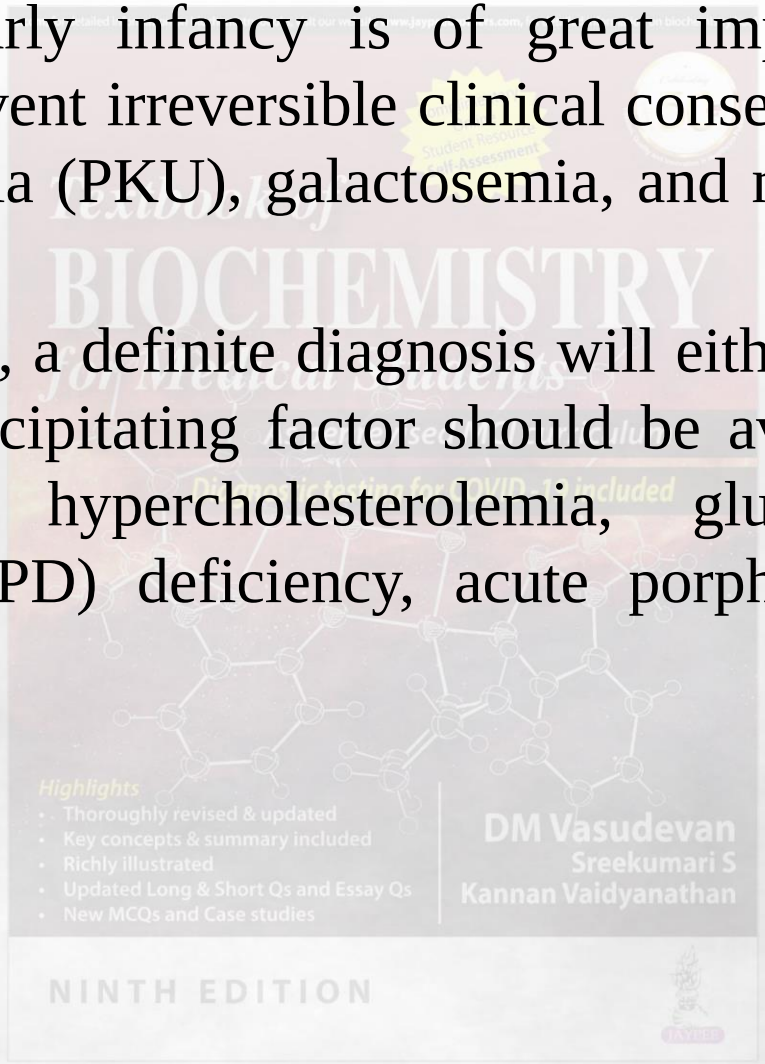
Garrod's tetrad
Alkaptonuria
Albinism
Pentosuria
Cystinuria

Garrod coined the word
"Inborn Errors of Metabolism" in 1909

Importance of Early Detection

Recognition in early infancy is of great importance because treatment may prevent irreversible clinical consequences or death, e.g. phenylketonuria (PKU), galactosemia, and maple syrup urine disease (MSUD).

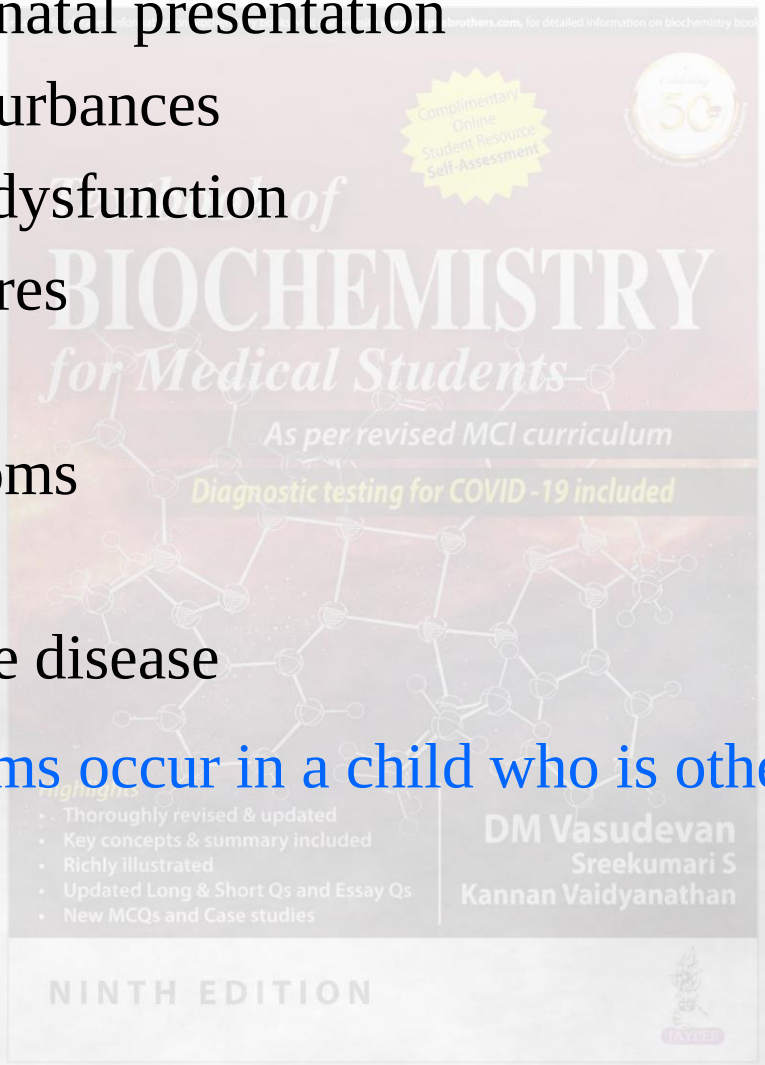
In some conditions, a definite diagnosis will either prevent further ill effects or a precipitating factor should be avoided. Examples include familial hypercholesterolemia, glucose phosphate dehydrogenase (GPD) deficiency, acute porphyrias, cystinuria, hemochromatosis.



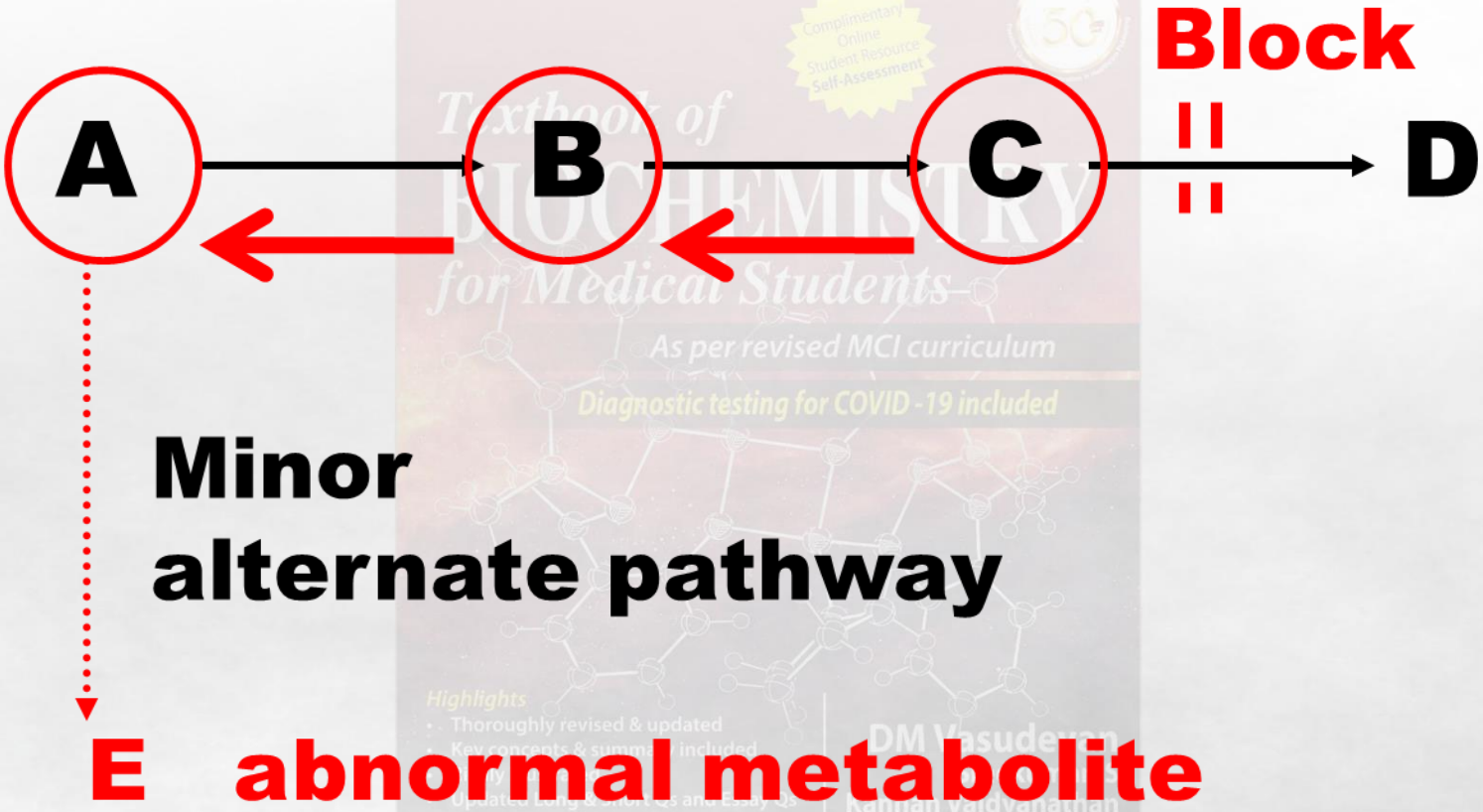
When to Consider a Metabolic Disorder

- Catastrophic neonatal presentation
- Biochemical disturbances
- Liver disease or dysfunction
- Neurologic features
- Cardiac features
- Skin, eye symptoms
- Coarse facies
- Signs of a storage disease

Often these symptoms occur in a child who is otherwise healthy at birth.

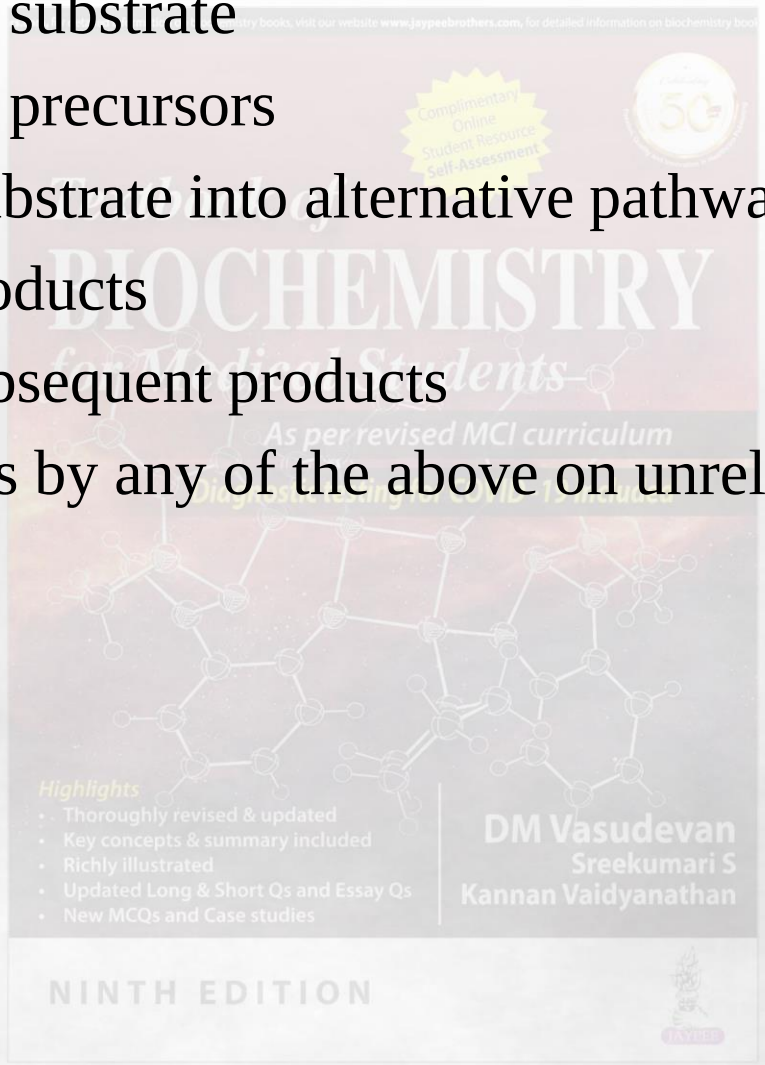


Metabolic Pathophysiology



Metabolic Pathophysiology

- Accumulation of substrate
- Accumulation of precursors
- Redirection of substrate into alternative pathways
- Deficiency of products
- Deficiency of subsequent products
- Secondary effects by any of the above on unrelated pathways

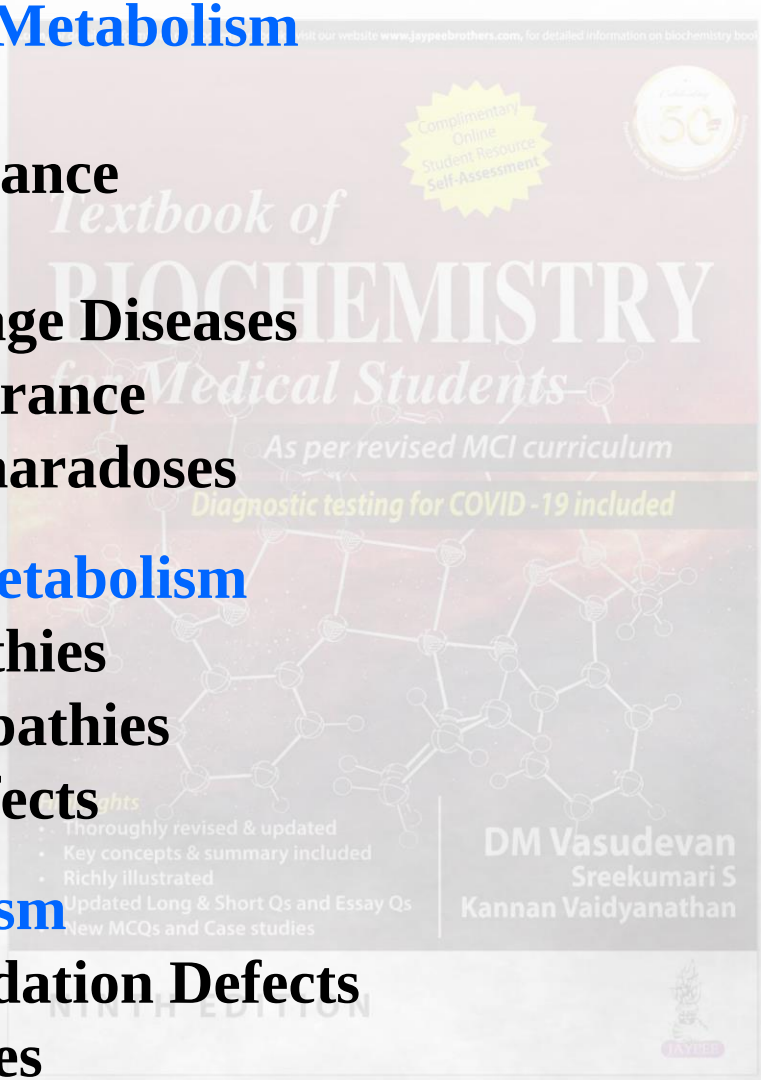


Classification of Inborn Errors of Metabolism

1. **Carbohydrate Metabolism**
   - Galactosemia
   - Lactose Intolerance
   - Lactic Acidosis
   - Glycogen Storage Diseases
   - Fructose Intolerance
   - Mucopolysaccharadoses

2. **Amino Acid Metabolism**
   - Aminoacidopathies
   - Organic Acidopathies
   - Urea Cycle Defects

3. **Lipid Metabolism**
   - Fatty Acid Oxidation Defects
   - Sphingolipidoses



4. Trace Metal Disorders

Menke's Kinky Hair Syndrome Wilson's Disease

5. Peroxisomal Disorders

Adrenoleucodystrophy

6. Lysosomal Storage Disorders

Niemann-Pick Disease Gaucher's Disease

7. Disorders of organic acid metabolism

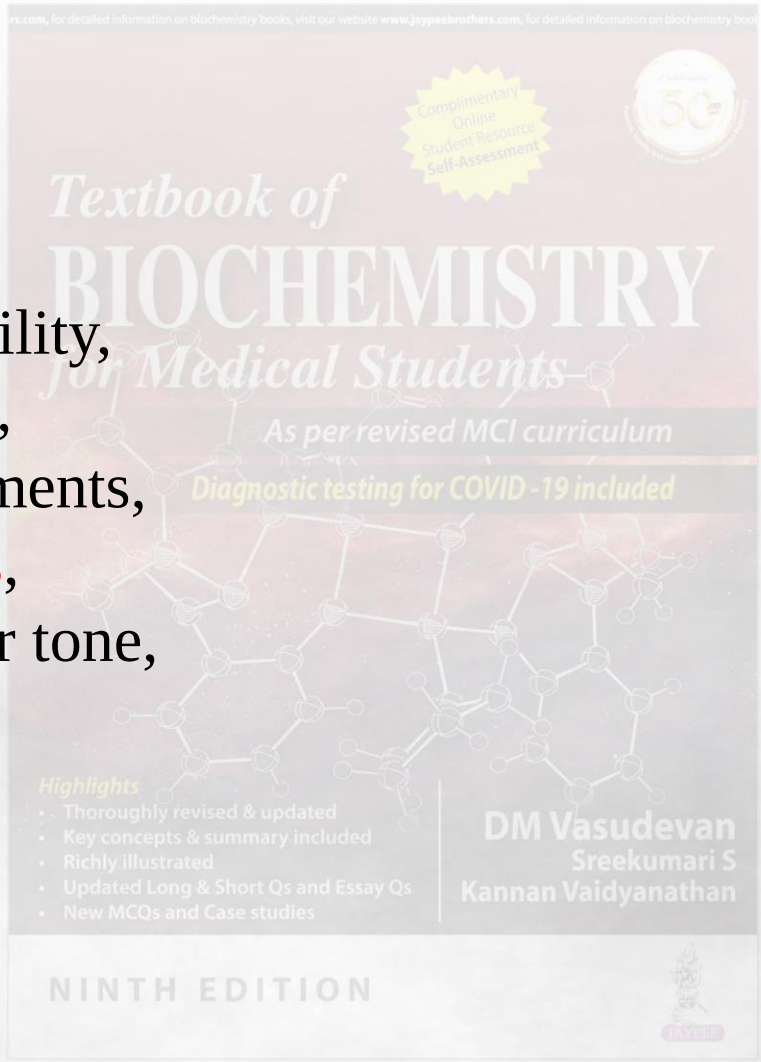
Alkaptonuria Branched chain organic acidurias Propionic aciduria, methylmalonic aciduria Defect in lysine oxidation: 2-keto adipic acidemia and glutaric acidemia Gamma glutamyl cycle disorders

Lactic acidemias Mitochondrial fatty acid oxidation disorders

Oxidative phosphorylation disorders

Common Symptoms of IMDs

Poor feeding,
Vomiting,
Diarrhoea,
Dehydration
Temperature instability,
Reduced heart beat,
Involuntary movements,
Irritability, seizures,
Abnormal muscular tone,
Skin rashes,
Seizures
Mental retardation



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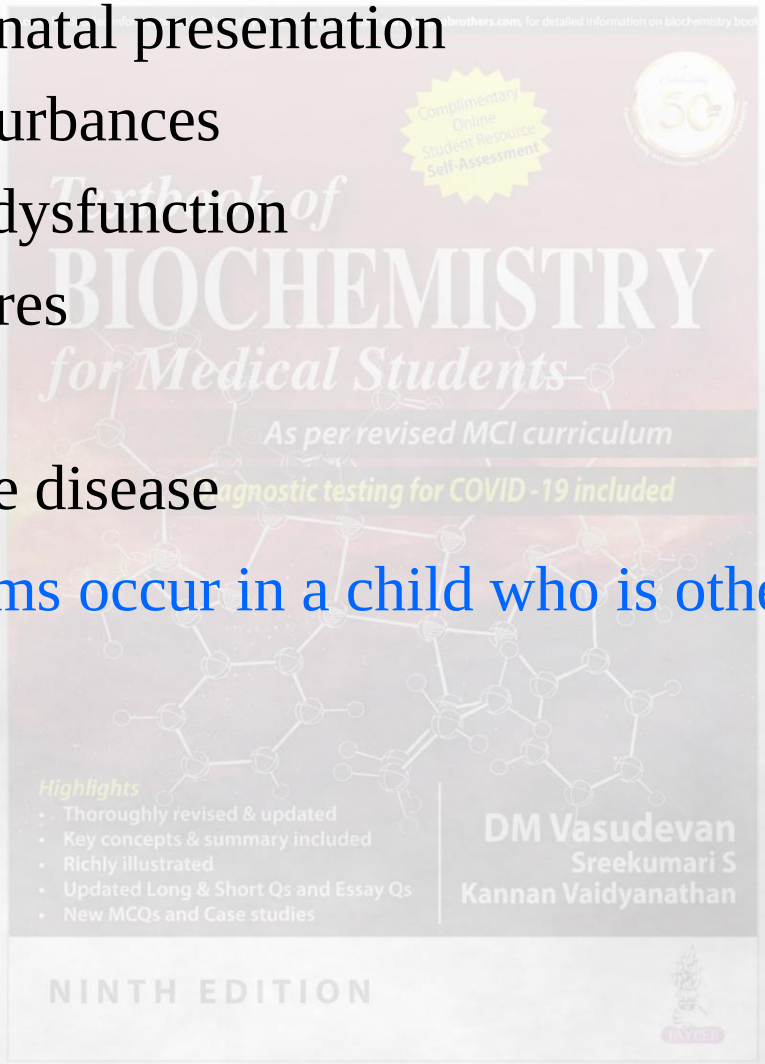
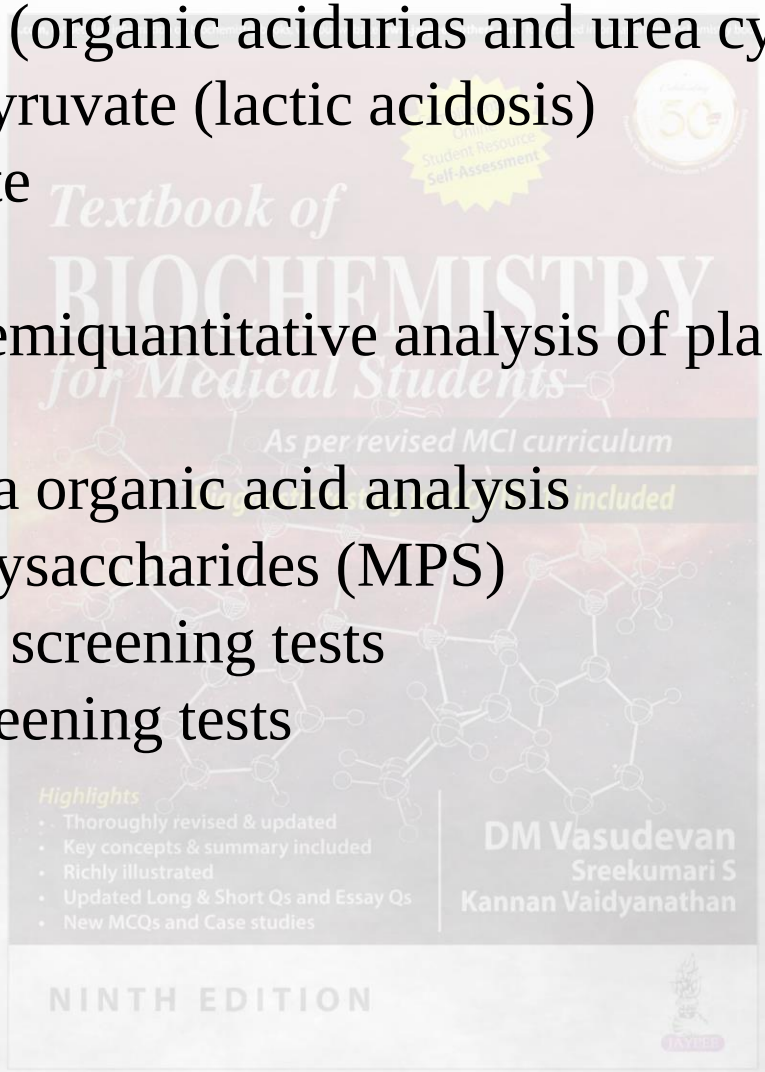


Studies Directed at The Classification of Disease Processes

1. Plasma ammonia (organic acidurias and urea cycle disorders)
2. Plasma lactate, pyruvate (lactic acidosis)
3. 3-hydroxybutyrate
4. Free fatty acids
5. Quantitative or semiquantitative analysis of plasma and urine amino acids
6. Urinary or plasma organic acid analysis
7. Urinary mucopolysaccharides (MPS)
8. Oligosaccharides screening tests
9. Galactosemia screening tests



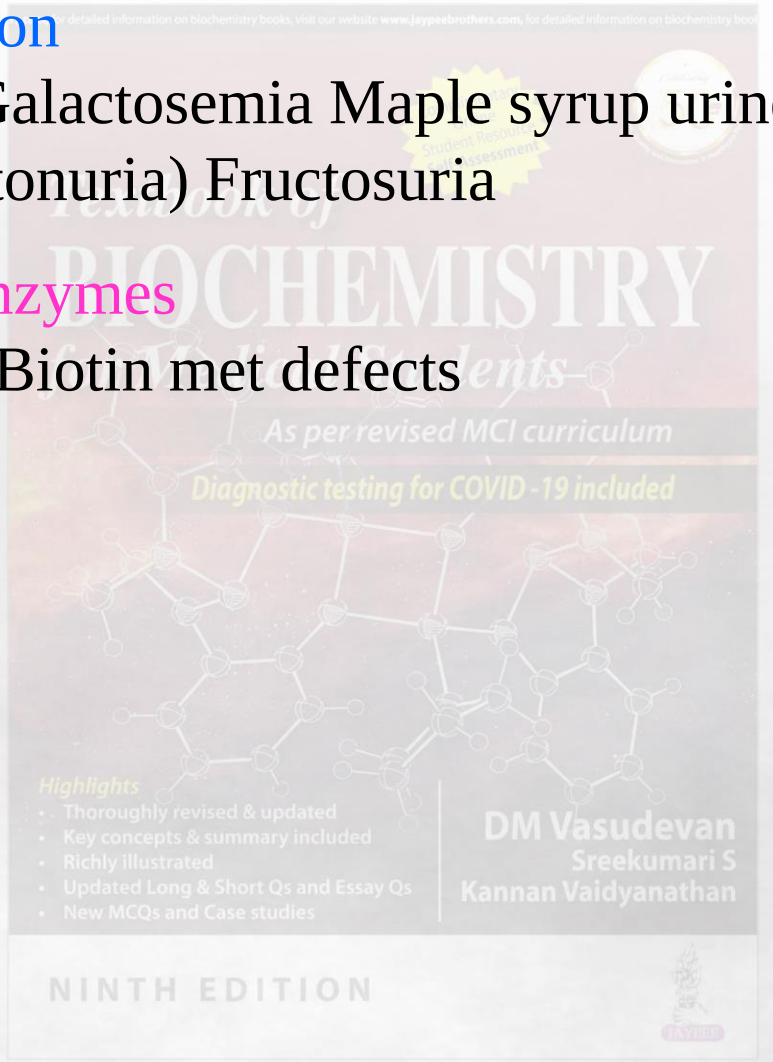
Therapeutic Modalities

Substrate Deprivation

Phenyl Ketonuria Galactosemia Maple syrup urine disease (branched chain ketonuria) Fructosuria

High doses of co-enzymes

Cobalamin defects Biotin met defects



Enzyme replacement therapy

- Gaucher- alpha glucosidase
- Fabry– alpha galactosidase
- Pompe's; Hurler's

Inhibition of substrate synthesis

- Glyco-sphingo-lipidoses

Bone marrow transplant

- Mucopolysaccharidoses
- Leukodystrophy
- Niemann-Pick

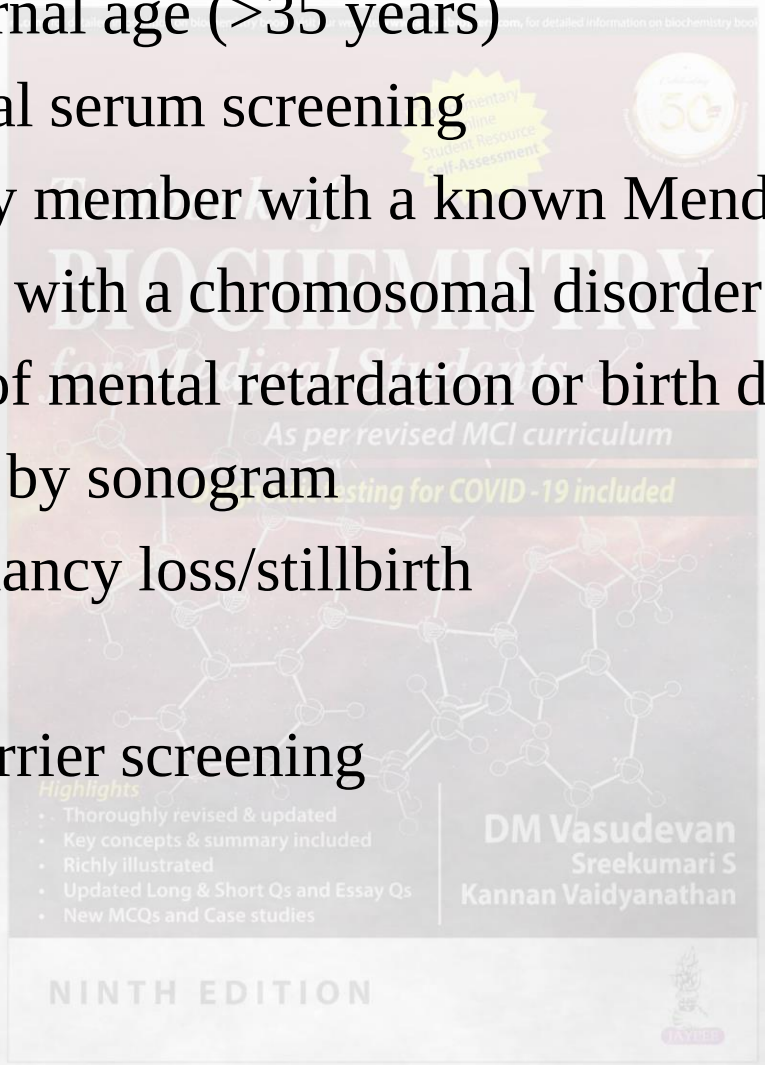
Liver transplant

- Wilson's disease
- Alpha-1 antitrypsin deficiency
- Crigler-Najjar syndrome

Gene therapy

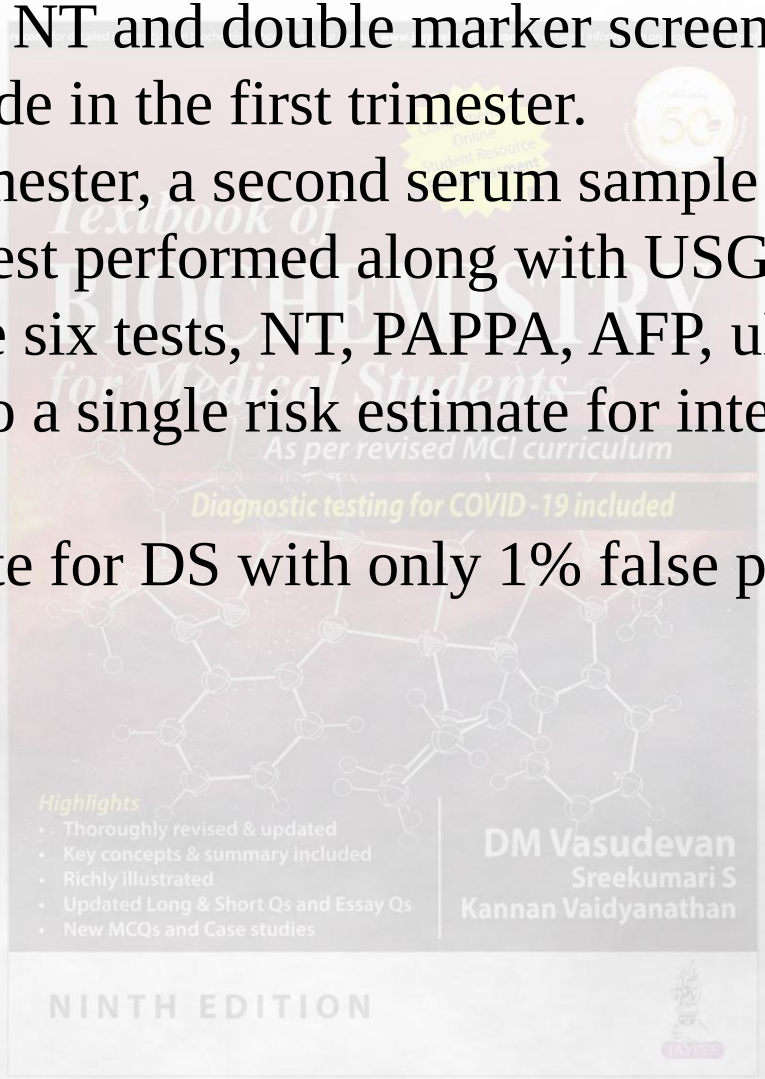
Common Medical Indications for a Referral to a Genetic Counselor

1. Advanced maternal age (>35 years)
2. Positive maternal serum screening
3. Patient or family member with a known Mendelian disorder
4. Prior pregnancy with a chromosomal disorder
5. Family history of mental retardation or birth defect
6. Fetal anomalies by sonogram
7. Recurrent pregnancy loss/stillbirth
8. Infertility
9. Ethnic-based carrier screening
10. Consanguinity



Suggested protocol for Maternal Screening

1. Measurements of NT and double marker screening (PAPPA and hCG) are made in the first trimester.
2. In the second trimester, a second serum sample is drawn and triple/quadruple test performed along with USG.
3. Results for all the six tests, NT, PAPPA, AFP, uE3, hCG and DIA are combined into a single risk estimate for interpretation in the second trimester.
4. 85% detection rate for DS with only 1% false positive is achieved.

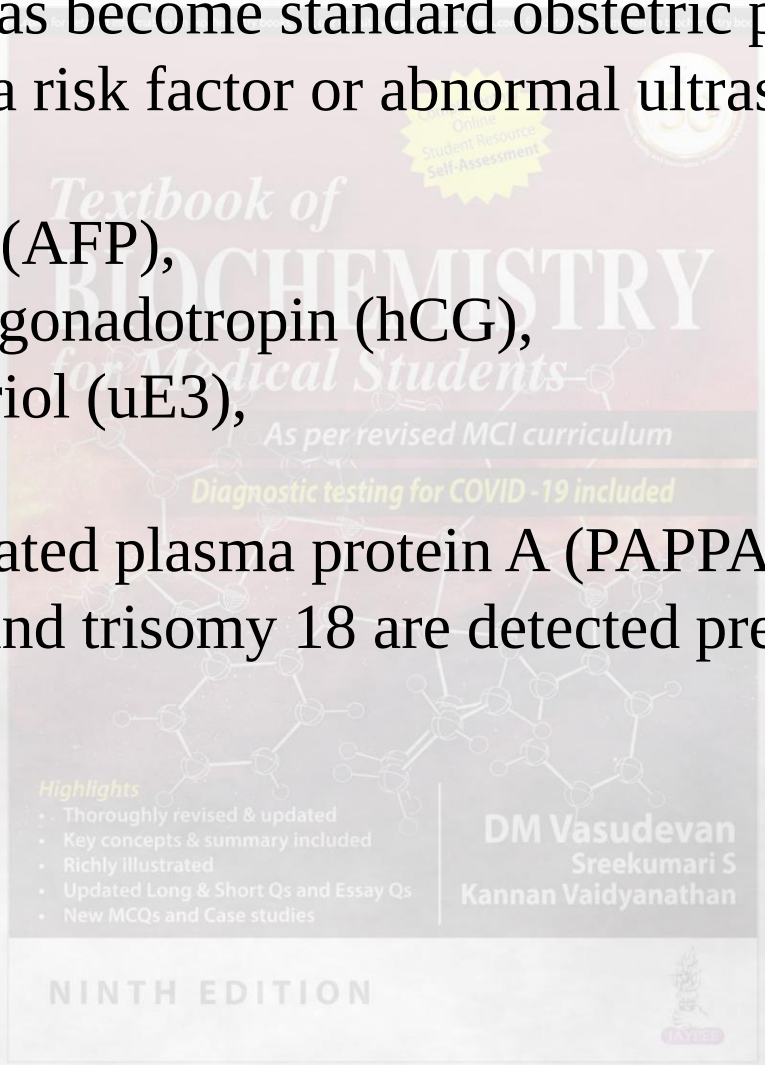


Maternal Serum Screening

Prenatal screening has become standard obstetric practice in all pregnancies having a risk factor or abnormal ultrasonographic (USG) findings.

1. alpha fetoprotein (AFP),
2. human chorionic gonadotropin (hCG),
3. unconjugated estriol (uE3),
4. inhibin, and
5. Pregnancy associated plasma protein A (PAPPA) are estimated.

NTDs, trisomy 21, and trisomy 18 are detected prenatally by these measurements.



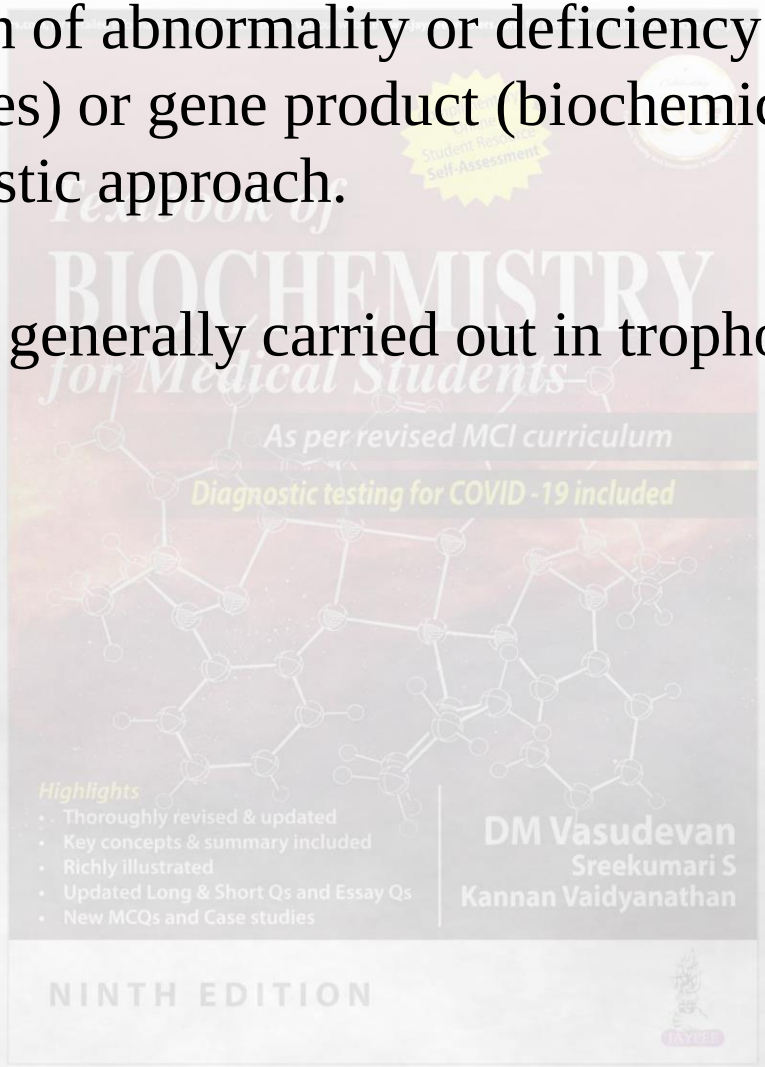
Maternal Serum Screening

Disorder	AFP	uE3	Beta-hCG	Inhibin A
Neural tube defect (NTD)	Increased	Normal	Normal	Normal
Down's syndrome	De-creased	De-creased	Increased	Increased
Trisomy 18	De-creased	De-creased	Normal	Normal

Enzyme Assays

Direct demonstration of abnormality or deficiency of the gene (molecular techniques) or gene product (biochemical techniques) is the preferred diagnostic approach.

Prenatal detection is generally carried out in trophoblast or amniotic fluid cell cultures.



Newborn Screening Programmes

1953: Treatment of PKU (H. Bickel)
1961: Guthrie Test, screening PKU
1970: Screening for galactosemia
1973: Maple syrup urine disease
1977: Homocystinuria
1978: Congenital hypothyroidism
1997: Congenital adrenal hypoplasia
1998: Introduction of Tandem mass spectroscopy

Expanded NB Screening in Europe by Tandem Mass-Spectometry

Country	# of diseases tested
Austria	20
Belgium	16
Denmark	18
Germany	10
Great Britain	2
Netherlands	11
Poland	11
Spain	9
Switzerland	2

In India

No comprehensive data available on occurrence

- Hospital based mass newborn screening program
- Mandatory screening of all newborns

Who needs awareness?

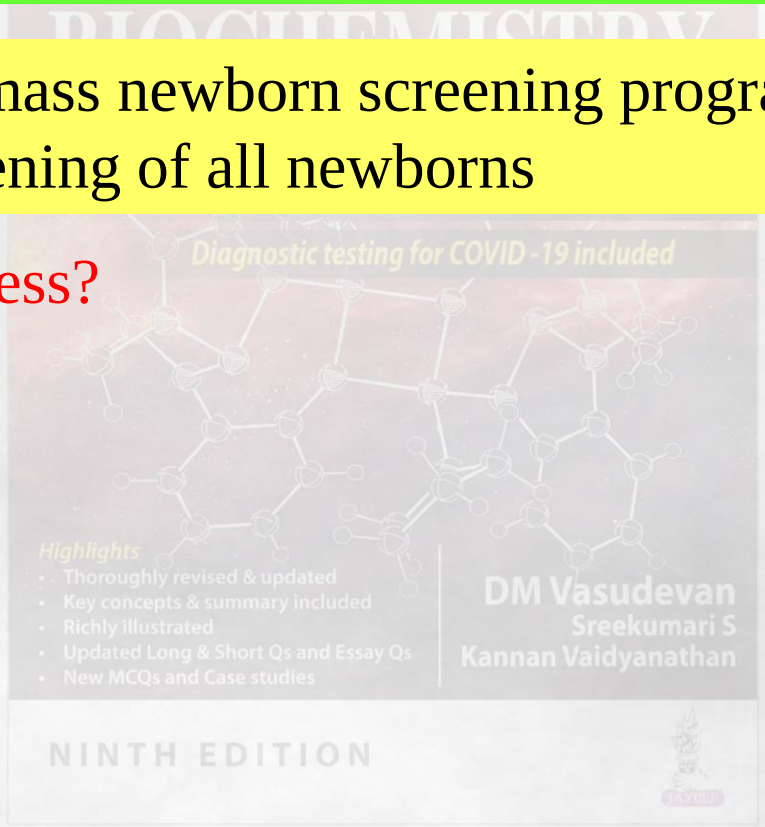
Clinicians

Mothers-to-be

Parents

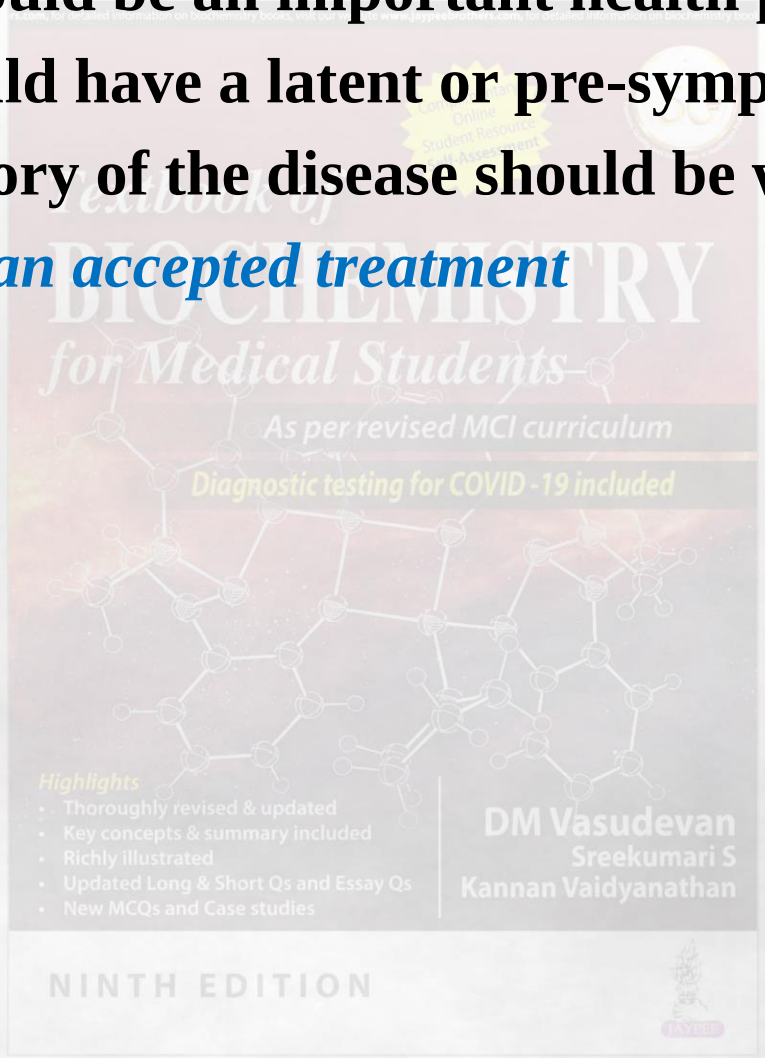
Hospital staff

General public



Criteria for Newborn Screening

- **The disorder should be an important health problem**
- **The disease should have a latent or pre-symptomatic stage**
- **The natural history of the disease should be well-known**
- ***There should be an accepted treatment***



Specimen Recommendations

1. Specimens should be obtained 24-48 hours of age.
2. In prematures, specimens should be repeated at 2 weeks, and perhaps again later depending on the degree of prematurity (2 months?).
3. Specimens should be obtained prior to transfusions.

Screening Tests

Offered to general population of patients; Healthy patients

Cheap

Easy

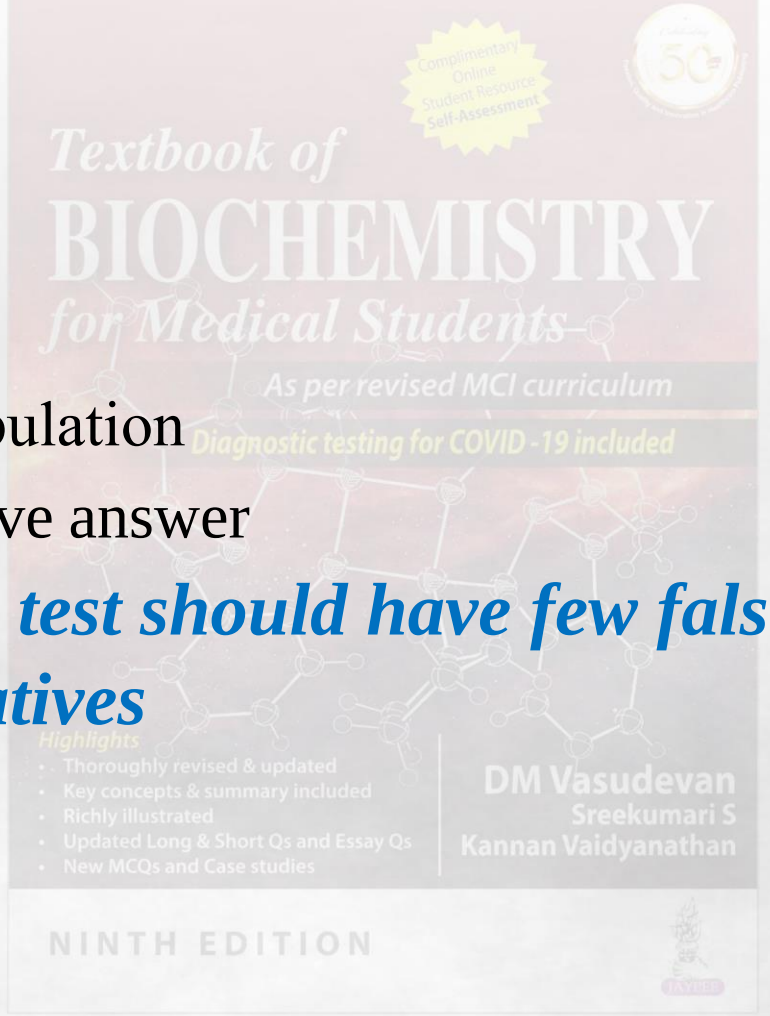
Reliable

Quick

Define "at risk" population

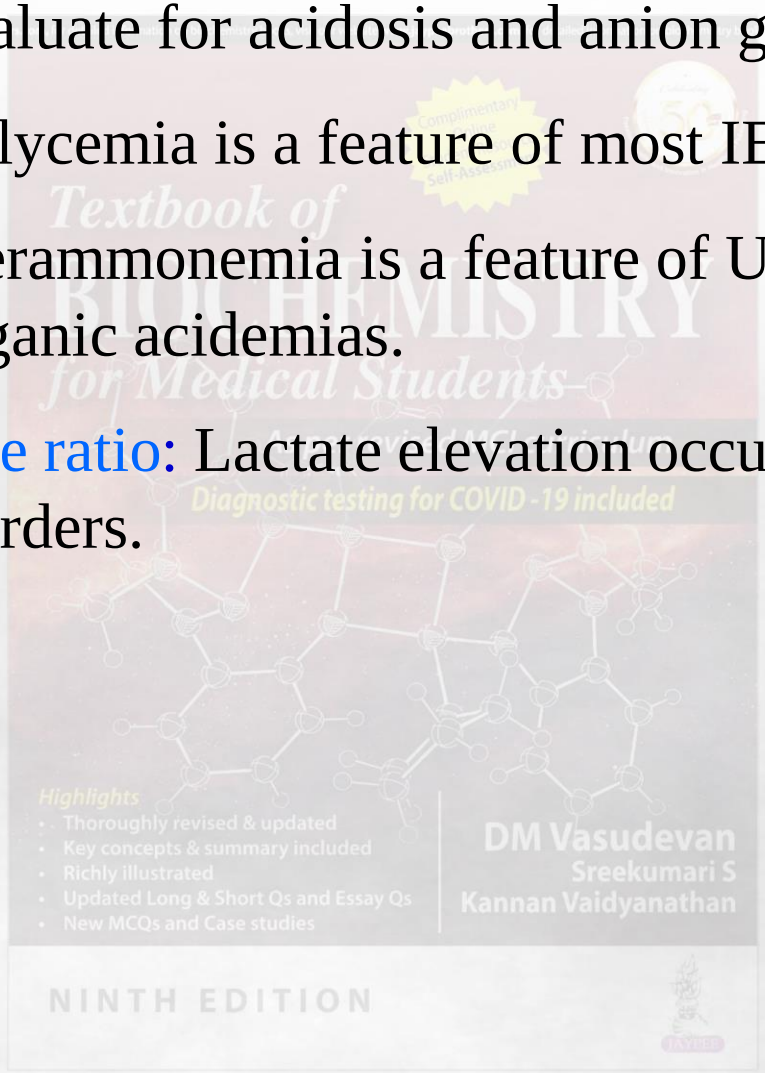
Do not give definitive answer

- ***The screening test should have few false positives and false negatives***



Initial Screening Tests

- Electrolytes: Evaluate for acidosis and anion gap.
- Glucose: Hypoglycemia is a feature of most IEM.
- Ammonia: Hyperammonemia is a feature of Urea metabolic diseases and Organic acidemias.
- Lactate/ Pyruvate ratio: Lactate elevation occurs in energy metabolism disorders.

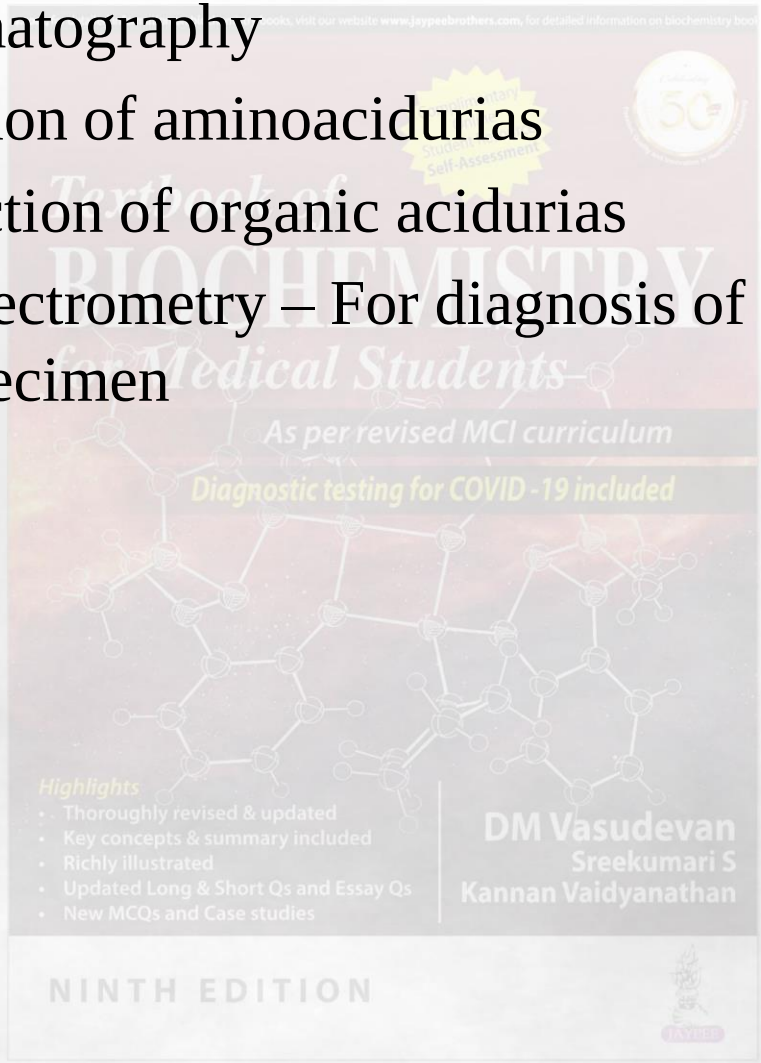


A Rapid Screening Test Kit

Urine Screening for about 35 IEM
Rothera's Test
Cyanide nitroprusside test
Ferric chloride test –
Benedict's test
DNPH test
CPC test
Ninhydrin test
Test for porphobilinogens
Test for methyl malonic acid Nitrosonaphthol test for tyrosine
Screening of all newborn babies Can be done in all small labs
If suspicious, send samples to central laboratories
Inborn errors are rare; But if undetected, mental retardation

Advanced Techniques for IEM

1. Thin layer chromatography
2. HPLC for detection of aminoacidurias
3. GC/MS for detection of organic acidurias
4. Tandem mass spectrometry – For diagnosis of >45 IEM using a single sample specimen



DNA Hybridisation / Probe Analysis

Advantages: Specific, Sensitive

Prenatal diagnosis possible,

Small sample volume.

Disadvantages: High Infrastructure cost

Requires dedicated trained personnel
Expensive consumables.\

DEFINITIVE DIAGNOSTICS TESTS

- Specific enzyme assays in leucocytes, plasma /serum or red cells.