

CLINICAL

BIOCHEMISTRY

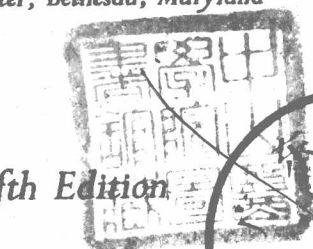
ABRAHAM CANTAROW, M.D.

*Professor of Biochemistry, Jefferson Medical College; Formerly
Associate Professor of Medicine, Jefferson Medical College and
Assistant Physician, The Jefferson Hospital, Philadelphia*

MAX TRUMPER, Ph.D.

*Formerly Lecturer in Clinical Biochemistry and Basic Science
Coordinator, Naval Medical School, National Naval Medical
Center, Bethesda, Maryland*

Fifth Edition



1955

COPYRIGHT, 1955,

Copyright, 1932, 1939, 1945 and 1949,

Preface to the Fifth Edition

Twenty-five years have elapsed since the authors undertook the preparation of the manuscript of the first edition of this book. At that time there was a lamentably wide gap between the literature of so-called "fundamental" biochemistry and physiology and that of clinical medicine. The majority of students, undergraduate and graduate, particularly practicing physicians, had great difficulty in bridging this gap and, consequently, in taking full advantage of current contributions to knowledge in the basic medical sciences.

The originally stated purpose of this book was to aid in making these correlations. This remains its purpose. However, the gap has narrowed considerably during the past twenty-five years. Clinicians generally have come to realize the truth of the statement by Claude Bernard, almost a century ago, that medicine does not end in the hospital, but rather begins there; that problems raised in the clinic should be passed to the laboratory for investigation and elucidation. Appreciation of this fact has led to closer integration of clinical medicine with the basic medical sciences, and a generation of clinicians has grown up whose routine reading matter is in the language of modern science.

It is possible now to discuss problems of acid-base balance and intermediary metabolism in relation to clinical disorders without much danger of employing terms and concepts incomprehensible to the majority of practicing physicians. In our experience, treatment of these subjects at the elementary level required twenty-five years ago is no longer necessary or desirable. For this reason, normal aspects of metabolism and biochemical mechanisms are discussed here more extensively than previously. It is hoped that this will provide a better basis for an understanding of aberrations of these processes in disease.

The text of the present edition has been virtually completely rewritten. Every chapter has been revised, and much new material has been added, particularly on the following topics: liver function; kidney function; plasma protein abnormalities; biological significance of nucleic acids; uric acid metabolism; porphyrin metabolism; biochemical aspects of diet; iodine metabolism; lipoproteins; fatty liver; potassium metabolism; acid-base balance; endocrine functional diagnosis, especially thyroid and adrenal.

As in previous editions, no attempt has been made to include material that has no relevance to biochemical approaches to the diagnosis or management of clinical disorders. This applies, for example, to most of the vitamins. One feature of previous editions has been eliminated; namely, the separate listings of biochemical abnormalities in various disease states. These were omitted mainly because the index provides this information in essentially the same form. Brief

PREFACE TO THE FIFTH EDITION

lists of selected reading references have been substituted for the previously longer bibliographies, and direct references have been omitted from the text. It is felt that the purposes of this book are served better by indicating authoritative reviews and monographic discussions of various important topics rather than a large number of original contributions.

As formerly, an attempt has been made to present controversial subjects in an impartial manner, supplemented wherever possible by an expression of personal opinion. There are few statements regarding the clinical significance of biochemical findings that are not supported by personal experience. Thanks are due to many friends and associates for helpful suggestions and advice, and to the publishers for their unfailing cooperation.

Jefferson Medical College,
Philadelphia

A. C.
M. T.

May, 1955

Preface to the First Edition

Modern advances in physiology and biochemistry have developed a need, not for another laboratory manual, but for a book designed to correlate established facts with problems encountered daily in internal medicine. The rapidity and magnitude of these developments have resulted in the growth of a highly specialized branch of laboratory medicine, namely, chemical pathology. The evolution of this specialty within a specialty has unfortunately tended to remove the clinician still further from a thorough understanding of those phases of internal medicine that require the assistance of the biochemical laboratory for their complete solution.

The remarkably fruitful researches of recent years in the fields of experimental physiology and pathology, by demonstrating the significance of biochemical observations in a constantly increasing number of abnormal states, have correspondingly increased their value to clinical medicine and surgery as well as to the laboratory. Modern practice demands the application of present knowledge regarding aberrations of endocrine, renal and hepatic function, abnormalities of organic and inorganic metabolism, nutritional defects, edema, dehydration, etc., in all branches of medicine as well as in pre- and postoperative treatment. The enormous increase in the use of chemicals in industry and in the treatment of disease and the growing appreciation of the possibly deleterious effects of such agents upon the organism have also increased the service that the biochemical laboratory may render to the clinician. The intelligent employment of these facilities will be of fundamental value in the increasingly important field of industrial toxicology.

The essential function of the laboratory is to supply the clinician with information which will complement that which he may obtain by other methods. Each patient presents a problem which cannot possibly be appreciated on the basis of dissociated laboratory studies. However, in order to take full advantage of the findings of the biochemist, the clinician must have a clear understanding of the significance and limitations of the results of laboratory investigation. This must be based upon an appreciation of the biochemical and physiologic factors involved in the preservation and alteration of organ and tissue function, for it may be stated, more truly than ever before, that physiology is the handmaid of medicine.

The progress made in the fields of biochemistry, metabolism, nutrition, colloidal and physical chemistry is based largely upon observations of a highly specialized and technical nature. This often renders the original literature unavailable to the majority of students and clinicians. As a result they usually either accept the brief interpretative statements made in most works on diagnosis by laboratory methods or they rely upon the chemical pathologist for an interpre-

tation of his findings. The position of the latter is little better than that of the clinician who is required to explain the significance of an enlarged liver in an individual whom he has not seen and concerning whose clinical history and physical condition he knows nothing. Experience in the laboratory and in the clinic has impressed the authors with the difficulty which students and physicians experience in bridging the wide gap between abstract biochemistry or physiology and clinical medicine. Books and articles in abundance have been written for and by specialists, but only a few have attempted to interpret specialized knowledge for the physician. The undergraduate student of medicine and the progressive physician wish to be familiar with the applications of biochemistry to clinical medicine and surgery. They should be as well acquainted with the limitations as with the significance of biochemical findings in any given case. This volume constitutes an attempt to supply this information.

Haldane has stated that the aim of physiology is to consider how the internal environment of the body is kept constant in spite of continual alterations in the external environment. The aim of this treatise is to consider how the internal environment of the body is altered by certain specific changes in tissue and organ physiology. It is further intended to indicate the manner in which the physician may best avail himself of information which can be obtained by biochemical studies. To this end the subject of functional diagnosis by chemical methods has been considered in considerable detail. With few exceptions, the technic of laboratory methods has not been discussed, being available in many admirable standard texts on that subject. The discussion has been restricted to those phases of biochemistry which are concerned with problems commonly encountered in clinical medicine and, therefore, purely abstract and theoretical considerations have been excluded.

A. C.
M. T.

Contents

CHAPTER I

Carbohydrate Metabolism	1
DIGESTION AND ABSORPTION	1
Fate of Absorbed Carbohydrate	2
Endogenous Sources of Glucose	3
UTILIZATION OF GLUCOSE	3
Storage	3
Oxidation	3
Conversion to Fat	4
Conversion to Other Carbohydrate	4
Conversion to Amino Acids	4
GENERAL PROCESSES IN CARBOHYDRATE METABOLISM	5
Anaerobic Metabolism (Glycolysis)	5
Aerobic Metabolism of Glucose	7
ROLE OF LIVER IN CARBOHYDRATE METABOLISM	8
Glycogenesis and Glycogenolysis	8
Gluconeogenesis	9
Assimilation of CO ₂	9
MUSCLE IN CARBOHYDRATE METABOLISM	10
Glycogenesis	10
Glycolysis	11
Muscle Contraction	11
INTERRELATION OF CARBOHYDRATE, LIPID, AND PROTEIN METABOLISM	12
ENDOCRINE INFLUENCES IN CARBOHYDRATE METABOLISM	14
Insulin	14
Adrenocortical Hormone.	16
Anterior Pituitary Factors	16
Epinephrine	17
Thyroid Hormone	17
Hyperglycemic Factor of Pancreas (HGF; Glucagon)	17
NORMAL POSTABSORPTIVE BLOOD SUGAR	17
Glucose in Body Fluids Other than Blood	18
Sugars Other than Glucose in Body Fluids.	19
REGULATION OF BLOOD GLUCOSE CONCENTRATION	20
Rate of Supply of Glucose to Blood	20
Rate of Removal of Glucose from Blood	21
Fundamental Regulatory Mechanism	22

NORMAL ALIMENTARY REACTION (ABSORPTIVE RESPONSE)	23
<i>Sugar Tolerance</i>	23
Intravenous Glucose Tolerance Test	25
Mechanism of Production of the Normal Glucose Tolerance Curve	25
Factors Influencing Absorptive Blood Sugar Response	27
The One-Hour, Two Dose Glucose Tolerance Test	29
EFFECT OF OTHER SUGARS	29
Galactose Tolerance	30
<i>Insulin Tolerance Test</i>	31
<i>Insulin-Glucose Tolerance Test</i>	31
<i>Epinephrine Tolerance Test</i>	31
<i>Phenomena Associated with Normal Alimentary Glucose Reaction</i>	32
Decreased Serum Phosphate	32
Decreased Serum Potassium	32
Increased Respiratory Quotient	32
ABNORMALITIES OF POSTABSORPTIVE BLOOD SUGAR LEVEL.	32
<i>Fasting Hyperglycemia</i>	32
Diabetes Mellitus	32
Hyperthyroidism	34
Increased Secretion of Epinephrine	35
Adrenal Cortical Hyperfunction	36
Hyperpituitarism	36
Anesthesia, Asphyxia, Hypnosis	36
Acidosis	37
Hepatic Disease	38
Miscellaneous	38
<i>Fasting Hypoglycemia</i>	38
Hyperinsulinism	39
Hepatic Disease	40
Adrenal Cortical Insufficiency	41
Anterior Pituitary Insufficiency	41
Hypothyroidism	42
Nervous System Disorders	42
Miscellaneous	42
ABNORMAL ALIMENTARY RESPONSE	42
<i>Exaggerated Response—Diminished Glucose Tolerance</i>	42
Diabetes Mellitus	43
Hepatic and Biliary Tract Disease	45
Hyperthyroidism	46
Hyperfunction of the Anterior Pituitary and Adrenal Cortex	46
Pregnancy	47
Miscellaneous	47
<i>Decreased Response—Increased Glucose Tolerance</i>	48
Hyperinsulinism	48

CONTENTS

Adrenal Cortical Insufficiency	49
Anterior Pituitary Hypofunction	51
Hypothyroidism	52
Miscellaneous	52
<i>Abnormal Insulin Tolerance</i>	53
<i>Abnormal Epinephrine Tolerance Test</i>	54
<i>Abnormal Tolerance for Other Sugars</i>	54
Abnormal Fructose Tolerance	54
Abnormal Galactose Tolerance	55
BLOOD LACTIC ACID AND PYRUVIC ACID	56
GLYCOGEN STORAGE DISEASES	57
Glycogen Storage Disease of Liver (von Gierke)	57
Glycogen Disease of the Heart	58
Galactosemia	58
Cirrhosis with Excessive Glycogen	58
EXCRETION OF SUGAR IN URINE	58
Mechanism of Glycosuria (Glucosuria)	58
Other Sugars in Urine	59
ABNORMAL URINE SUGAR	59
<i>Melituria</i>	59
<i>Tests for the Detection of Sugars</i>	59
Metallic Oxide Reduction Tests	59
Fermentation Test	60
Phenylhydrazine Reaction	60
Specific Rotation	60
Glycosuria	61
Nonhyperglycemic Glycosuria	61
Hyperglycemic Glycosuria	64
<i>Fructosuria</i>	65
<i>Pentosuria</i>	66
<i>Lactosuria</i>	67
<i>Galactosuria</i>	67
<i>Maltosuria</i>	67
DIABETES MELLITUS	67
<i>Experimental Diabetes Mellitus</i>	68
Total Pancreatectomy	68
Subtotal Pancreatectomy	69
Alloxan Administration	69
Administration of Adrenocortical Hormones	70
Anterior Pituitary Extracts	70
Thyroid Administration	70
Carbohydrate Metabolism in Hypophysectomized-Depan- creatized Animals	71
<i>Clinical Diabetes Mellitus</i>	71
Hyperglycemia	71

Decreased Carbohydrate Tolerance.	72
Glycosuria	73
Decreased Respiratory Quotient	74
Lipemia and Ketosis	74
Acidosis	75
Electrolyte and Water Balance	76
Negative Nitrogen Balance-Hypoproteinemia	77
Nitrogen Retention	78
REFERENCES	78

CHAPTER II

Lipid Metabolism	80
NATURE OF LIPIDS	81
Fats (Triglycerides)	81
Phospholipids (Phosphatides)	82
Glycolipids	84
Steroids.	84
Lipoproteins	85
DIGESTION AND ABSORPTION	86
METABOLISM OF FAT	88
Immediate Fate of Dietary Lipid	88
Anabolism and Catabolism of Fatty Acids	88
Anabolism and Catabolism of Lipids	90
Lipid Mobilization	90
ENDOCRINE INFLUENCES IN LIPID METABOLISM	91
Insulin	91
Adrenocortical Hormones	91
Anterior Pituitary Hormones	92
Thyroid Hormone	92
METABOLIC INTERRELATIONS OF LIPIDS, CARBOHYDRATES AND PROTEINS	92
KETOSIS	94
FAT IN FECES	96
FAT IN URINE	98
METABOLISM OF PHOSPHOLIPIDS	98
Turnover	98
Catabolism	99
METABOLISM OF STEROLS AND BILE ACIDS	99
Catabolism and Excretion of Cholesterol; Conversion to Bile Acids.	100
TRANSPORT OF LIPIDS	101
State of Lipids in Blood: Lipoproteins	101
Postabsorptive Plasma Lipid Concentration.	102

CONTENTS

Influence of Food and Nutrition	104
Influence of Age and Sex	105
Pregnancy	105
DEPOSITION AND STORAGE OF LIPIDS	105
Role of Liver in Lipid Metabolism	105
Fatty Liver and Lipotropism	106
LIPOIDOSIS, XANTHOMATOSIS	109
I. <i>Primary (Essential) Xanthomatosis</i>	110
A. Normocholesterolemic Type	110
B. Hypercholesterolemic Type	110
C. Combined Types A and B	110
II. <i>Xanthomatosis Secondary to Hyperlipemia</i>	110
ABNORMALITIES OF PLASMA LIPIDS	110
PLASMA LIPOPROTEIN ABNORMALITIES AND ATHEROSCLEROSIS	111
Increase in Sf 12-20 Lipoproteins	112
Beta-Lipoprotein Increase	112
Effect of Heparin	113
HYPERCHOLESTEROLEMIA	113
Diabetes Mellitus	113
Anesthesia	115
The Nephrotic Syndrome	115
Hepatic and Biliary Tract Disease	116
Hypothyroidism	117
Atherosclerosis	118
Xanthomatosis	118
Idiopathic (Essential) Hyperlipemia	119
Miscellaneous	119
HYPOCHOLESTEROLEMIA	120
Anemia	120
Hepatic Disease	120
Infection	121
Hyperthyroidism	121
Inanition	122
Terminal States	122
Miscellaneous	123
REFERENCES	123

CHAPTER III

Protein Metabolism	124
DIGESTION AND ABSORPTION	125
Dynamic State	126
Metabolic Pool	127

OVER-ALL METABOLISM OF PROTEIN	128
Nitrogen of the Food	129
Nitrogen of the Body	129
Excretion of Nitrogen	129
Nitrogen Balance	129
Essential Amino Acids	130
Biological Value of Proteins	131
Dietary Protein Requirements	132
INTERMEDIARY METABOLISM	134
Protein Turnover	134
General Pathways of Protein Metabolism	134
INTERRELATIONS OF THE METABOLISM OF PROTEINS AND OTHER FOOD- STUFFS	138
ENDOCRINE INFLUENCES IN PROTEIN METABOLISM	140
Growth Hormone	140
Androgen	140
Adrenal 11-Oxysteroids	140
Insulin	141
Thyroxine	141
NITROGENOUS CONSTITUENTS OF THE BLOOD	141
<i>The Plasma Proteins</i>	141
Identity and Properties	141
Metabolism	144
Functions	145
NONPROTEIN NITROGEN	148
Urea	148
Uric Acid	148
Creatinine.	148
Amino Acids	148
Ammonia	149
Undetermined Nitrogen (Rest Nitrogen)	149
NITROGEN EXCRETION	149
Urea	149
Uric Acid	150
Creatine and Creatinine	150
Amino Acids	151
Ammonia	151
ABNORMAL PROTEIN METABOLISM	152
Total Plasma (Serum) Protein	152
Fibrinogen	153
Albumin	154
Globulins	158
<i>Globulin Reactions</i>	163
Zinc Sulfate Turbidity	163
Formol-Gel Reaction	163

CONTENTS

Colloidal Gold Curve	163
CO ₂ Saturation Test	164
Cephalin-Cholesterol Flocculation Test	164
Thymol Turbidity Test	164
Other Globulin Reactions	165
<i>Protein Diagnostic Tests for Cancer</i>	165
NONPROTEIN NITROGEN OF BLOOD	166
Urea Nitrogen	166
Uric Acid	168
Creatinine.	168
Amino Acid Nitrogen	168
Ammonia	169
Undetermined or Residual Nitrogen	169
Total Nonprotein Nitrogen	169
ABNORMAL URINARY NITROGEN	170
<i>Protein in Urine</i>	170
The Nature and Origin of Urinary Proteins	170
Functional Albuminuria	172
Organic Albuminuria	173
Quantity of Protein in Urine	176
Other Proteins in Urine	177
<i>Urinary Nonprotein Nitrogen</i>	179
Urinary Urea	179
Uric Acid in Urine	180
Creatine and Creatinine in Urine	180
Amino Acids in Urine	182
Ammonia in Urine	185
Negative Nitrogen Balance in Disease	186
Urinary Nitrogen Partition	187
<i>Congo Red Test for Amyloidosis</i>	188
REFERENCES	189

CHAPTER IV

Nucleic Acid Metabolism 190

INTERRELATIONS OF METABOLISM OF NUCLEIC ACIDS WITH OTHER

FOODSTUFFS 191

BIOLOGICAL SIGNIFICANCE OF NUCLEIC ACIDS 192

Viruses 193

Chromosomes—Genes 193

"Transforming Substance" of Bacteria 194

Role of Nucleic Acids in Mutation and Carcinogenesis 194

Role of Nucleic Acids in Protein Synthesis 195

FREE NUCLEOTIDES OF BIOLOGICAL IMPORTANCE	196
Adenylic Acid System	196
Coenzymes	196
DIGESTION AND ABSORPTION	196
INTERMEDIARY METABOLISM	197
Nonnitrogenous Constituents	197
Purines and Pyrimidines	197
Uric Acid	199
REFERENCES	202

CHAPTER V

Metabolism of Hemoglobin and Porphyrins	203
Synthesis of Porphyrins	204
Synthesis of Hemoglobin	205
Catabolism of Hemoglobin	206
"Abnormal" Hemoglobins	206
HEMOGLOBINEMIA	207
ABNORMAL HEMOGLOBIN DERIVATIVES	208
Methemoglobin	208
Sulfhemoglobin.	209
Carboxyhemoglobin	209
Hematinemia	209
PORPHYRIA AND PORPHYRINURIA	210
Porphyria	210
Acquired Porphyrinurias	211
REFERENCES	212

CHAPTER VI

Biochemical Aspects of Diet	213
Caloric Content of Diet	215
Dietary Carbohydrates	216
Dietary Lipid	217
Dietary Protein	218
REFERENCES	223

CHAPTER VII

Calcium and Inorganic Phosphate Metabolism	224
ABSORPTION	224
BLOOD CALCIUM AND PHOSPHATE	225

CONTENTS

Parathyroid Hormone	226
Vitamin D	228
Plasma Proteins	228
Plasma Phosphate	228
Acid-Base Equilibrium	228
Miscellaneous	229
DEPOSITION AND MOBILIZATION OF BONE MINERALS	229
Mineralization of Bone.	229
Mobilization of Calcium	230
MISCELLANEOUS FACTORS	231
EXCRETION	231
CALCIUM AND PHOSPHORUS REQUIREMENT	232
CALCIUM CONTENT OF OTHER BODY FLUIDS	232
ABNORMAL SERUM CALCIUM	233
<i>Hypercalcemia</i>	233
Hyperparathyroidism	233
Hypervitaminosis (Vitamin D)	234
Multiple Myeloma	235
Neoplastic Disease of Bone	235
Acute Bone Atrophy	236
Kidney Disease	236
Miscellaneous	236
<i>Hypocalcemia</i>	236
Hypoparathyroidism	236
Pseudohypoparathyroidism	238
Vitamin D Deficiency (Rickets and Osteomalacia)	238
Steatorrhea (Sprue, Celiac Disease)	238
Hunger Osteopathy	238
Nephrosis	238
Nephritis	239
Maternal Tetany	239
Magnesium, Phosphate, Oxalate and Citrate Tetany	239
Acute Pancreatitis	239
Alkalosis	240
ABNORMAL URINE CALCIUM	240
<i>Increased Urinary Calcium</i>	240
Hyperparathyroidism	240
Hyperthyroidism	241
Acidosis	241
Hypervitaminosis D	241
Idiopathic Hypercalciuria	241
<i>Decreased Urinary Calcium</i>	241
Hypoparathyroidism	241
Vitamin D Deficiency	241
Hypothyroidism	242

Ingestion of Bases	242
Miscellaneous	242
ABNORMAL FECAL CALCIUM.	242
HYPERPHOSPHATEMIA	242
Hypervitaminosis	242
Hypoparathyroidism	242
Renal Failure	242
Healing Fractures	243
HYPOPHOSPHATEMIA	243
Rickets	243
Osteomalacia	244
Idiopathic Steatorrhea	244
Hyperparathyroidism	244
Fanconi Syndrome	244
Increased Carbohydrate Utilization	245
ABNORMAL URINARY PHOSPHATE	245
DISTURBANCES OF BONE FORMATION AND MINERALIZATION	246
REFERENCES	247

CHAPTER VIII

Phosphatase Activity 248

NORMAL SERUM ALKALINE PHOSPHATASE	249
<i>Skeletal Diseases</i>	249
Rickets	250
Hyperparathyroidism (Generalized Osteitis Fibrosa Cystica)	250
Osteitis Deformans (Paget's Disease)	251
Miscellaneous Bone Disorders	251
ALKALINE PHOSPHATASE ACTIVITY IN JAUNDICE, HEPATIC AND BILIARY DISEASE	251
Obstructive and Hepatocellular Jaundice	251
Other Biliary Tract Conditions	252
MISCELLANEOUS CONDITIONS	252
SERUM ACID PHOSPHATASE	252
REFERENCES	254

CHAPTER IX

Magnesium Metabolism 255

ABSORPTION AND EXCRETION	255
BLOOD MAGNESIUM	255
Abnormal Serum Magnesium	256