KUGELMASS

BIOCHEMICAL DISEASES

Chemical Pediatrics

BIOCHEMICAL DISEASES (CHEMICAL PEDIATRICS)

By

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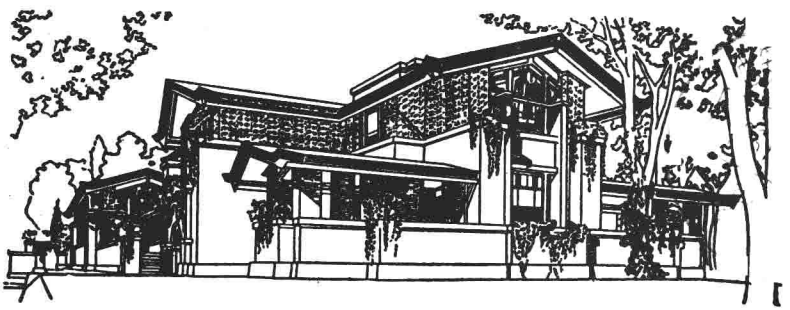

CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • U.S.A.

Published and Distributed Throughout the World by

CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.
NATCHEZ PLANTATION HOUSE
735 North Atlantic Boulevard, Fort Lauderdale, Florida, U.S.A.

Library of Congress Catalog Card Number: 64-14060

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Printed in the United States of America
P-4

Foreword

OUR LIVING CHEMISTRY SERIES was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarships, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Kugelmass of New York correlates and integrates the major developments and current trends in biochemical medicine. Biochemistry is not only deepening our grasp of fundamental life phenomena and influencing the thinking about disease processes but transforming empirical practice into a clinical science by substituting facts for appearances, measurements for approximations and demonstrations for impressions. The analytical approach is reenforcing the organismic in unravelling the chemical nature of disordered life processes to bring basic knowledge and investigative experience to the bedside. The author's biochemical sys-

tem of clinical medicine thus aims to organize clinical material according to chemical viewpoints with particular emphasis on underlying mechanism as the basis for management. The classification of biochemical diseases is clinical; Part I presents the communicative disorders involving the nervous and endocrine systems; Part II, the systemic disorders involving the nutritional, metabolic, and hemopoietic systems; and Part III, the regional disorders involving end organ systems. Most of the abnormal processes are viewed as uncompensated biochemical disorders of self-regulating mechanisms with loss of homeostasis responsive to metabolic reversal. We know more than we understand, but once chemical understanding is clear, clinical action is easy. Harmonious fusion of chemistry and medicine keeps their independence equal, dependence mutual and obligation reciprocal for optimal diagnosis for optimal treatment for optimal health.

"Whoever thinks a faultless piece to see
Thinks what ne'er was, nor is, nor e'er shall be."

I. NEWTON KUGELMASS, M.D., PH.D., SC.D., *Editor*

Preface

DISEASE IS A TERM derived from old French desaise or dis-ease, universally differentiated from health except by the ancient Stoics and modern cultists. Actually, disease and health are complimentary functions on a single scale with the elusive zero point at the extreme left corresponding to finite death from pathological disorders; the intangible limit at the extreme right corresponding to optimal health from physiological reserves; and all the gradations between these extremes corresponding to latent or manifest disease. We may thus consider disease as a dynamic state comprising equilibrial elements no different from those of health, though less useful in body functions. Pope rebelled against it in the epistle to his physician: "This long disease, my life." Disease recurs in basic forms with incidence and prevalence varying from time to time and from place to place, for we change, not the diseases, as we learn to recognize what was formerly imperceptible on the scale of life in health and disease.

The concept of disease varies with changes in knowledge, but two ideas dominate medical history; first, that disease is a distinct clinical entity in an individual subject; and second, that disease is a biochemical deviation from the normal range of health in every patient. The former is simple but often misleading emphasizing the disease and its pathognomonic manifestations, while the latter is rational yet comprehensive, stressing the patient and his pattern of illness. Deviations from norms represent heritable disorders attributable to mutant genes, progressive consequences of acquired dysfunctions, or marked extremes of distributions of disturbing traits. Such a dynamic concept of bodily deviation emerges from the chemical advances in clinical medicine during the last half-century which elevate everyday

practice from dogmatism to dynamicism. We know much more about disease than we understand; but as biochemical medicine clarifies our understanding, rational procedure augments the effectiveness of management.

The mechanism of disease was envisaged first as a disturbance of the soul; later, of the tissues; and finally, of the cells as the dynamic unit of the body. In health, its chemical components and environs are maintained remarkably constant by regulatory processes of the autonomatic nervous system, endocrine and other systems; in disease, the membrane is the first cell structure to become altered in function with consequent increase in permeability, loss of cytoplasmic components into the circulation, and disturbance in the physicochemical equilibria of the cells. Disordered cell function precipitates the initial symptoms in the gradual or abrupt transition from health to disease but early recognition of this reversible stage requires deep-seated understanding of the underlying process. Biochemical disease involves chemical alteration in cell metabolism by pathogenic agents. Interference with any chemical reaction in the dynamic equilibria will affect the entire system, alter the behavior of the cell and initiate the biochemical lesion with characteristic systemic effects. Disease embraces not only the biochemical lesion but the body's defensive response to the pathological agent which threatens the integrity of the organism; its form and function are like matter and energy, merely two aspects of the same thing in medicine.

Clinical descriptions of biochemical syndromes are stages away from the bedside picture. The process by which theory is transmuted into practice is polydimensional often eluding two-dimensional clarification. There are no pure syndromes but proximate entities with latent or manifest signs and symptoms reflecting permutations and combinations of chemical derangements in the patient. The diagnosis involves a biographical method and its technique of clinical history, and a nosographic method and its technique of the complete examination. The newer methods of laboratory investigation of ever-increasing precision and refinement increase reliance on the knowledge demanded from these special means of study of clinical problems even though

the data is collected by fallible human beings committing errors in technique and interpretation. The clinical study and management of the patient thus becomes the fundamental responsibility of the physician not only for the control of organ disease but for the restitution of well-being of the total organism, based on biochemical understanding of the local and systemic processes of life. The science of medicine rests on knowledge of clinical techniques; the art of medicine, on the skill of utilizing them in the service of the patient.

The mechanism and management of biochemical diseases of infancy and childhood was conceived in a series of chemical lectures in the Department of Pediatrics of the Yale University Medical School and continued at the Department of Pediatrics of the Fifth Avenue Hospital in New York. The present work describes, analyzes and interprets biochemical changes in the organism in health and disease for clinical application to everyday practice. The chemical illustrations were prepared by Mr. Leon Schlossberg of the Johns Hopkins Medical School and the clinical illustrations by Mrs. Marion L. Weston of New York. Grateful acknowledgement is further due to my editorial colleagues whose cooperation after criticism was as the sun after a shower; to my secretary, Miss Virginia Chaffin-Schmidt; to my assistant, Mrs. Bertha K. Donson; and to Charles C Thomas, Publisher, for their forebearance during the monograph's long gestational period.

I.N.K.

Biochemical Discoveries

Twentieth Century

1902—Hofmeister and E. Fischer formulated proteins as polypeptides.
1903—Takamine and Aldrich isolated epinephrine.
1904—Stolz and Dakin synthesized epinephrine.
1905—Knopp discovered β-oxidation
1910—Bayer and Dale synthesized norepinephrine.
1911—Baumann discovered diiodotyrosine in thyroid.
1912—Wieland advanced the theory of dehydrogenation in biologic oxidations.
1915—Kendall crystallized thyroid hormone.
1919—Doisy isolated crystalline estrogen.
1921—Banting and Best discovered insulin.
1922—Ruznick formulated the isoprene rule as a building principle of numerous natural products.
1924—Keilin rediscovered cytochromes; Hanson and Collip extracted parathormone; Haworth formulated sugars as pyranoses.
1925—Svedberg determined the molecular weights of proteins with the ultracentrifuge.
1926—Jansen and Donath isolated the first vitamin, thiamine; Sumner first crystallized an enzyme.
1927—Harrington and Barger synthesized thyroxin.
1928—Stricker and Grieter discovered prolactin.
1929—Lohmann, Fiske and Subarrow discovered adenosine triphosphate; Warburg characterized the respiratory enzyme as a hemin compound.
1930—Butenandt, Doisy, Laquer and Reichstein isolated steroid hormones.
1932—Marrian determined the structure of estrone and estriol; Warburg and Theorell discovered the yellow enzyme.
1933—Embden and Meyerhof evolved the new scheme of glycolysis and alcoholic fermentation.

1934—v. Euler, Theorell and Warburg discovered the connection between vitamins and coenzymes.
1935—Rose isolated threonine as the first essential amino acid; Butenandt and Ruzicka synthesized androgens from cholesterol; Dodds synthesized estrogens.
1936—Selye unravelled the "alarm reaction."
1937—Krebs, Knopp and Martius formulated the citric acid cycle.
1938—Braunstein and Kritzmann discovered transamination; Reichstein synthesized desoxycorticosterone.
1939—Fleming, Florey, Chain and Johnson isolated the first antibiotic, penicillin.
1942—Richter and Astwood discovered antithyroid drugs.
1943—Butenandt and Kuhn discovered the mechanism of the action of gene factors through enzymes.
1944—Avery isolated the pneumoccal transformation factor as a desoxyribonucleic acid.
1948—Schneider and Hoogenboom introduced centrifugation for the isolation of cell fragments; Sarett synthesized cortisone.
1950—Lipman and Lynen elucidated "active" acetate.
1951—Pauling evolved the helical structure of proteins.
1952—Gross and Pitt-Rivers discovered triiodothyronine; Simpson and Tait discovered aldosterone.
1953—Sanger elucidated the structure of insulin.
1954—Horecker and Dickens discovered the pentose phosphate cycle in glucose breakdown.
1955—Watson and Crick prepared the helical model of nucleic acids.
1957—Gierer and Schramm proved the infectivity of pure virus nucleic acids.
1958—Lynen demonstrated isopentenyl pyrophosphate as active isoprene.
1959—Rasmussen and Aurbach prepared parathormone peptides.
1960—Nirenberg and Ochoa decoded the base code of DNA of nucleic acids of the living cell.
1961—Hofmann synthesized ACTH peptide.
1962—Burnet evolved the mechanism of autoimmune disease; Lowry studied the chemistry of single neurons.
1963—Yanofsky correlated mutations with the amino-acid sequence in enzymes as a function of activity.
1963—Karl Ziegler and Guilio Natto evolved the structure of body macromolecules.
1964—Crick demonstrated the composition, structure and amino-acid sequence of protein crystals by x-ray analysis

Abbreviations

A	anion component of a salt
Å	Angstrom unit
Acetyl-**CoA**	**Ac**etyl Coenzyme A
AcG	**acc**elerator globulin
ACTH	**Adr**enocorticotropic hormone
ADH	**antidi**uretic hormone
ADP	**adeno**sinediphosphate
AE	**apoen**zyme
A/G	**ratio** of albumin to globulin
AHF	**anti**hemophilic factor
AHG	**anti**hemophilic globulin
AMP	adenosinemonophosphate
ATP	adenosine triphosphate
AT-10	dehydrotachysterol
ATP-ase	adenosinetriphosphatase
at wt	atomic weight
B	cation component of a salt
BAL	2,3 dimercaptopropanol
$B^+HCO_3^-$	bicarbonate of salt of any cation
BMR	basal metabolic rate
BP	blood pressure
B^+P^-	catonic salt of serum protein
$\gamma\gamma$	micromicrograms $=$ g $\times 10^{-12}$
cal	calories
centi-	10^{-2}, i.e., one hundredth
CF	citrovorum factor
CHO	carbohydrate
CNS	central nervous system
CoA	coenzyme A
CoI	coenzyme I
COP	colloid osmotic pressure
$c\mu$	cubic microns
[ ]	concentration

CRP	C-reactive protein
deci-	10^{-1}, i.e., one-tenth
D/N	dextrose-nitrogen ratio
DNA	deoxypentosenucleic acid
DOC	deoxycorticosterone
DOCA	deoxycorticosterone acetate
DPN	diphosphopyridine nucleotide
DRNA	deoxyribonucleic acid
e	electron
ECF	extracellular fluid
ECG	electrocardiogram
Eq	equivalents
ESR	erythrocyte sedimentation rate
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide
FSH	follicle-stimulating hormone
g	gram or grams
GDH	glucose dehydrogenase
GSH	glutathione, reduced
HA	fixed acid of any sort
Hb	hemoglobin
HbO_2	oxyhemoglobin
HCG	human chorionic gonadotrophin
HDP	hexose diphosphate
HGF	hyperglycemic-glycogenolytic factor
HHb	reduced hemoglobin
HPr	serum protein as buffer anion
ICF	intracellular fluid
ICSH	interstitial cell-stimulating hormone
IU	international unit
KHB	potassium salt of reduced hemoglobin
$KHbO_2$	potassium salt of oxyhemoglobin
kilo	10^3, i.e., one thousand
l	liter
LDH	lactate dehydrogenase
LF	labile factor
LH	luteotropic hormone
log	logarithm to the base 10
LTH	luteotropic hormone
M	mol, molar, or gram-molecular weight
m	meter

MCD	mean corpuscular diameter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCT	mean corpuscular thickness
MCV	mean corpuscular volume
mega	10^6, i.e., one million
mEq	milliequivalents
mg	milligram
micro-	10^{-6}, i.e., one millionth
milli-	10^{-3}, i.e., one thousandth
mM	millimoles
min	minute
mol	gram-molecule
mOsm	milliosmol
MSH	melanocyte-stimulating hormone
$m\mu$	millimicron
$m\mu g$	millimicrograms
mol wt	molecular weight
MW	molecular weight
N	normal, or one equivalent per liter
NAAP	N-acetyl-4-aminoantipyrine
NaPr	sodium salt of serum protein
NPN	non-protein nitrogen
OP	osmotic pressure
Osm	osmol
P	pressure
P	phosphate group
P	proton
PABA	para-aminobenzoic acid
PBI	protein-bound iodine in blood
PGA	pteryglutamic acid
PGH	pituitary growth hormone
PCO_2	partial pressure of carbon dioxide
pH	negative logarithm of H^+
pK	negative logarithm of a dissociation constant
ppm	parts per million
Pr	protein
PSP	phenolsulfonephthalein
PTA	plasma thromboplastin antecedent
PTC	plasma thromboplastin component
PTF	platelet thromboplastic factor

PTH	parathyroid hormone
PVP	polyvinylpyrrolidone
r	roentgen
RBC	red blood cells
RNA	ribonucleic acid
rpm	revolutions per minute
RQ	respiratory quotient
sec	second
S_f	Svedberg of flotation
SPCA	serum prothrombin conversion accelerator
sp gr	specific gravity
SF	stable factor
S_{20}	sedimentation constant in Svedbergs at 20° C.
STH	somatotropic hormone
STP	standard temperature and pressure
T	absolute temperature
TEM	triethylene melamine
TEPA	triethylenophosphoramide
TPN	triphosphopyridine nucleotide
TSH	thyroid-stimulating hormone
U	unit
μ	micron (10^{-3} mm)
μg	microgram (10^{-3} mg)
$\mu\mu$	micromicron (10^{-9} mm)
UDP	uridine diphosphate
V	volume
VDM	vasodepressor material
VEM	vasoexcitor material
vol %	volumes per cent
WBC	white blood cell

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