

The Principles and Practice of DIAGNOSTIC ENZYMOLOGY

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Diagnostic Enzymology

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Preface

The extensive use of enzyme activity determinations as aids to the diagnosis of disease in hospital laboratories all over the world is one of the most dramatic developments in modern medicine. From small beginnings early in the present century when the digestive enzymes were studied in blood and urine, clinical enzymology has grown to the stage when the chemical laboratories of our major hospitals perform several hundred enzyme tests each working day. Such progress is due partly to the recognition that the activities of certain enzymes may change in certain disease states and partly to the development of procedures convenient enough for routine use.

In the 1930's the serum acid and alkaline phosphatase were found to have diagnostic applications in diseases of the prostate, bone and liver and thanks to the introduction of relatively simple techniques for the determination of their activities by King, Bodansky and others, these tests soon found their way into the repertoire of clinical laboratories. Recent advances in our knowledge of the chemistry of alkaline phosphatase have led to ever-increasing interest in the clinical value of this enzyme. Perhaps the most important single factor leading to the rapid development of clinical enzymology has been the introduction of the ultra-violet spectrophotometer which has permitted the activities of NAD^+ - and NADP^+ -dependent enzymes to be determined conveniently and with acceptable precision. This has undergone further refinement so that today a number of semi-automated instruments are available which enable a single technician to make hundreds of determinations in a few hours.

The introduction of serum transaminase measurements to confirm the diagnosis of myocardial infarction by Wróblewski and his colleagues in 1954 led to the recognition that intracellular enzymes may be released into the plasma from damaged tissues generally. This single event acted as a trigger to fire the imaginations of clinicians and clinical biochemists all over the world and enzyme tests for the investigation of diseases of the liver, skeletal muscle, gastro-intestinal tract, blood, brain, kidney and other tissues soon followed. In 1962, my *Introduction to Diagnostic Enzymology* was published in an attempt to review the diagnostic applications of enzyme determinations. Although many of the recommendations made are still valid, the kind

reception accorded this work, the suggestions of many clinical and laboratory colleagues, and the wealth of new material which has since become available, persuaded me to write the present book with the aim of summarizing the current situation. It is hoped that it will prove of interest to clinicians, especially cardiologists, gastroenterologists, and paediatricians, as well as to pathologists and clinical biochemists, particularly those preparing for the examination in chemical pathology for Membership of the Royal College of Pathologists and for the Mastership in Clinical Biochemistry.

The task of writing this monograph unaided, however, proved beyond my resources, and I am most grateful to a number of friends and colleagues, all acknowledged experts in their respective fields, who kindly agreed to contribute chapters.

The book is divided into two parts, the first six chapters are concerned with biochemical considerations while the remaining twelve are devoted to the clinical applications of enzyme activity measurements. As in the earlier book, the first chapter summarizes relevant basic enzymology. This is followed by chapters dealing with the oxidoreductases, transferases, hydrolases, lyases and isomerases of diagnostic interest. The classification of enzymes recommended by the International Union of Biochemistry has been followed throughout. Part I is completed by a chapter on clinical enzyme assay methods which it is hoped will be of interest to laboratory workers responsible for deciding the procedures to be used for routine purposes.

Part II begins with a chapter in which the rationale of clinical enzymology is discussed in the light of the results of some recent personal researches. Chapter 8, devoted to enzyme tests in myocardial infarction and other cardiovascular diseases, is followed by one contributed by Dr S. B. Rosalki on enzymes in diseases of skeletal muscle. Dr Rosalki is also the author of Chapter 10, in which he discusses enzyme tests in liver and hepatobiliary diseases. The role of enzyme procedures in the investigation of diseases of the alimentary tract, contributed by Dr A. H. Gowenlock, is followed by a consideration of enzyme tests in diseases of bone by Dr D. W. Moss. The occurrence of a number of haematological diseases due to the congenital deficiency of certain enzymes is the topic discussed by Dr E. Beutler. Succeeding chapters are devoted to enzyme tests in diseases of the urinary tract, malignant diseases and pregnancy. Professor Brenda Ryman then discusses the role of enzyme procedures in the diagnosis and classification of the glycogen storage diseases, and finally Dr D. N. Raine tackles the enormous number of congenital enzyme anomalies, most of which are manifested in infancy or childhood. I have endeavoured to ensure that the treatment is as comprehensive as possible within the space allowed, and at the same time have tried to eliminate unnecessary repetition by the use of appropriate cross-references.

In addition to thanking my co-authors I should like to express my gratitude to members of the staff of Charing Cross Hospital and its associated Medical School for their help. In particular I wish to thank Dr J. Swale,

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J. H. Wilkinson
London, W6
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Contents

Preface	vii
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Part I Biochemical Considerations

Chapter 1	
The structure and actions of enzymes	3
The nature of enzymes	5
Enzyme terminology and classification	9
Occurrence of enzymes in tissues	12
Isoenzymes	14
Determination of enzyme activities	16
Kinetics of enzyme reactions	29

Chapter 2	
Chemistry of enzymes of diagnostic interest	
I. Oxidoreductases	43
Alcohol dehydrogenase	43
Iditol (sorbitol) dehydrogenase	45
Lactate dehydrogenase	46
Malate dehydrogenase	54
Isocitrate dehydrogenase	56
6-Phosphogluconate dehydrogenase	58
Glucose 6-phosphate dehydrogenase	60
Glyceraldehyde phosphate dehydrogenase	63
Glutamate dehydrogenase	63
Diamine oxidase	65
Glutathione reductase	66
Caeruloplasmin (copper oxidase)	67

Chapter 3

Chemistry of enzymes of diagnostic interest

II. Transferases	80
Ornithine carbamoyltransferase	80
Transketolase	83
γ -Glutamyltransferase	85
Aspartate transaminase	87
Alanine transaminase	93
Hexokinase	95
Pyruvate kinase	96
Creatine kinase	96
Adenylate kinase (myokinase)	101
Phosphoglucomutase	102
Hexose 1-phosphate uridylyltransferase	104

Chapter 4

Chemistry of enzymes of diagnostic interest

III. Hydrolases	116
Lipase	116
Acetylcholinesterase and cholinesterase	119
Alkaline phosphatase	129
Acid phosphatase	141
5'-Nucleotidase	144
Glucose 6-phosphatase	147
Fructose 1,6-diphosphatase	148
Arylsulphatase	148
Amylase	149
β -Glucuronidase	154
Leucine aminopeptidase	156
Alanine aminopeptidase	158
Pepsin	158
Trypsin and chymotrypsin	160
Arginase	163
Guanine deaminase (guanase)	165
Adenosine diaminase	166

Chapter 5

Chemistry of enzymes of diagnostic interest

IV. Lyases and isomerases	187
Fructose biphosphate aldolase	187
Fumarate hydratase	190

Aconitate hydratase	191
Enolase	191
Argininosuccinate lyase	192
Triose phosphate isomerase	193
Glucose phosphate isomerase	193

Chapter 6	
Clinical enzyme assay methods	199
Two-point assays	199
Methods involving continuous monitoring	203
Automated methods	206
Storage of specimens	212
Quality control and standardization	214

Part II Clinical Enzymology

Chapter 7	
General considerations	221
The rationale of serum enzyme tests	221
Normal ranges	230
Enzyme activities in body fluids other than serum	235
Enzymes in cells and tissues	236

Chapter 8	
Myocardial infarction and other cardiovascular diseases	241
Myocardial infarction	242
Other cardiovascular diseases	254

Chapter 9	
Enzymes in diseases of skeletal muscle	263
S. B. Rosalki	
Serum enzymes in myopathy	263
Other genetically determined myopathies	275
Inflammatory myopathy	276
Traumatic myopathy	277
Toxic muscle damage	282
Myopathies associated with endocrine or metabolic disease	286
Neurogenic muscle disease	287
Isoenzymes in muscle disease	289
Conclusion	292

Chapter 10	
Enzyme tests in diseases of the liver and hepatobiliary tract	303
S. B. Rosalki	
Classification of hepatic disease	303
Serum enzyme changes in liver disease	305
Transaminase and alkaline phosphatase changes in individual liver diseases	306
Hepatitis	306
Infectious mononucleosis	312
Drug-induced and chemical hepatitis	314
Chronic hepatitis	316
Hepatic cirrhosis	318
Cholestatic liver disease	320
Hepatic neoplasms	326
Other infiltrative liver diseases	328
Hepatic effects of alcohol	329
Isoenzymes in liver disease	332
Other serum enzymes in liver diseases—'hepatocellular' enzymes	338
Other 'cholestasis' enzymes	340
 Chapter 11	
Diseases of the alimentary tract	361
A. H. Gowenlock	
The main enzymes concerned in alimentary tract function	362
Gastrointestinal tract enzymes in plasma and urine	375
Enzymology of diseases of the salivary glands	378
Enzymology of gastric disease and peptic ulceration	378
Enzymology of diseases of the exocrine pancreas	381
Enzymology of disease of the small intestine	387
Enzymology of diseases of the large intestine	391
 Chapter 12	
Enzyme tests in diseases of bone	399
D. W. Moss	
Relationship of alkaline phosphatase to calcification of bone	399
Early studies on serum alkaline phosphatase in bone disease and development of assay methods	401
Normal serum alkaline phosphatase activity and changes during physiological bone development	402
Changes in serum alkaline phosphatase activity in bone disease	404
Isoenzymes of serum alkaline phosphatase in bone disease	413
Serum acid phosphatase in bone disease	418

Chapter 13	
Enzyme tests in haematological diseases	423
E. Beutler	
Enzyme anomalies of the red cell	423
Enzyme defects which result in drug sensitivity—G6PD deficiency	424
Hereditary nonspherocytic haemolytic anaemia	430
Hereditary spherocytosis	441
Hereditary methaemoglobinaemia	442
Alterations in red cells which do not bear a cause-and-effect relationship to red cell disease	444
Acquired red cell abnormalities	444
Addendum (J. H. Wilkinson)	455
Plasma enzymes in anaemia	455
Enzyme tests in leukaemia	459
 Chapter 14	
Enzyme tests in diseases of the urinary tract	461
Enzyme activities in the kidney	461
Filtration of enzymes	463
Urinary enzymes	464
Serum enzymes	469
 Chapter 15	
Malignant diseases	474
Glycolytic enzymes in cancer	475
Phosphatases in cancer	482
Other enzyme studies in cancer	487
 Chapter 16	
Serum enzyme tests in pregnancy	494
Heat-stable alkaline phosphatase	494
Cystyl-aminopeptidase	496
Other aminopeptidases	497
Diamine oxidase	498
Other serum enzyme tests	499
 Chapter 17	
The glycogen storage diseases	503
Brenda E. Ryman	
Structure of glycogen in glycogen storage disease	506
Site of enzyme defect: choice of tissue for enzyme assay	506

Useful screening tests for the differential diagnosis of glycogen storage disease	507
Methodology for tissue examination	510
Assays on tissues	511
Leucocytes and erythrocytes preparation	513
Enzyme units: normal values	513
 Chapter 18	
Congenital enzyme anomalies	518
D. N. Raine and A. Westwood	
Disorders of amino-acid metabolism	522
Disorders of carbohydrate metabolism	529
Urea cycle disorders	534
Mucopolysaccharidoses	536
Lipidoses	540
Miscellaneous anomalies	550
 Index	569

Part I

Biochemical Considerations

Chapter 1

The structure and actions of enzymes

The use of enzymes in diagnosis dates back to the beginning of the present century when Wohlgemuth introduced his procedure for measuring urinary amylase activity. Together with the serum amylase and serum lipase, this test soon found applications in confirming the diagnosis of acute pancreatitis, but although a number of refinements of the techniques were introduced, little progress was made in applying enzyme measurements to the investigation of disease until about 1930 when the potentialities of the serum alkaline phosphatase were recognized. Earlier, Robison (1922) had demonstrated phosphatase activity in bone extracts and subsequently in blood plasma (Martland and Robison, 1926). Largely through the efforts of Bodansky and King, convenient methods for the determination of serum alkaline phosphatase were developed, and these enabled this enzyme to be used in the study of bone disease and later in post-hepatic obstructive jaundice.

Meanwhile, Warburg and his colleagues made the important observation that in malignant tumours glucose was metabolized mainly by glycolysis in contrast to the oxidative processes in most normal tissues (Warburg and Minami, 1923), but many years were to elapse before this discovery could be turned to practical advantage. In 1943, Warburg and Christian found increased levels of aldolase and phosphohexose isomerase in the serum of tumour-bearing rats, an observation applied to human serum by Bodansky (1954) and by Bruns and Jacob (1954).

1954 proved to be a watershed in the history of clinical enzymology for in that year LaDue *et al.* reported transient elevations in the serum glutamate oxaloacetate transaminase (now more correctly known as aspartate transaminase) after an episode of myocardial infarction. This highly significant discovery had a tremendous impact on the development of the subject, since it demonstrated that intracellular enzymes could be released into the circulation