

CONTRIBUTION OF BIOCHEMISTRY TO MEDICINE: MEDICAL BIOCHEMISTRY AND CLINICAL BIOCHEMISTRY

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Summary

Medical biochemistry is biochemistry related to human health and disease. Its applicative arm is clinical chemistry, a field that focuses on the methodology and interpretation of chemical tests performed to support diagnosis and treatment.

This chapter first defines the scope of medical biochemistry, as currently described to undergraduate students. It then describes the constantly changing scope of clinical biochemistry.

Historical development of chemistry and biochemistry is outlined. While the beginnings of chemistry date to the 17th and 18th centuries, biochemistry emerged in the late 18th

and early 19th century. The article discusses how, with increasing relevance of biochemistry to clinical practice, clinical biochemistry evolved, and how it consolidated in the 1940s as an autonomous field. The heterogeneous origins of clinical biochemistry are emphasized: one stream representing evolution from academic physiological chemistry, and the other from clinical medicine and morbid pathology.

Methodological developments have always been the principal driving force in clinical biochemistry. It first emerged as research-focused field, and it subsequently evolved into an increasingly applicative discipline. The article goes on to reflect on the role of clinical laboratories in contemporary healthcare. It makes the point that contemporary clinical biochemistry tends to support research, rather than lead academically. On this background, the importance of research vs. service provision for the future of clinical biochemistry as a discipline is discussed.

The appearance of laboratories as spaces dedicated to science is also addressed, and the recent change in these spaces caused by the challenges of large-volume testing and laboratory automation is considered.

Finally, the issues associated with integration of clinical biochemistry with other laboratory disciplines at both technical and academic level are addressed, and the relevant geographical differences highlighted.

While describing the roots and achievements of medical and clinical biochemistry, the achievements of key investigators are followed to demonstrate the importance of individual thought as well as of that of 'schools' formed by the leading individuals.

1. What Is Medical Biochemistry

Chemistry is a science of matter. Biochemistry focuses on the studies of biological matter. Previously, biochemistry was referred to as 'biological chemistry' or 'physiological chemistry' (a term that is still occasionally used for the sake of tradition). In France the term 'biochimie medicale' is used as an equivalent of physiological chemistry. Similarly, in some Polish universities, departments of physiological biochemistry were named 'medical biochemistry' (biochemia lekarska). Molecular biology is commonly regarded as part of biochemistry and this is reflected in the names of a number of scientific societies and journals.

In this article medical biochemistry will be regarded as biochemistry (and molecular biology) applied to human organism in health and disease. Medical biochemistry seeks to advance the understanding of chemical structures and processes that constitute health and disease, and underlie transformations between these two states.

Clinical biochemistry is an important applied sub-discipline of medical biochemistry, , also known under the names of clinical chemistry, pathological biochemistry or chemical pathology (Figure 1). Clinical biochemistry is concerned with methodology and interpretation of biochemical tests performed on body fluids and tissues, to support diagnosis, treatment and monitoring of disease.

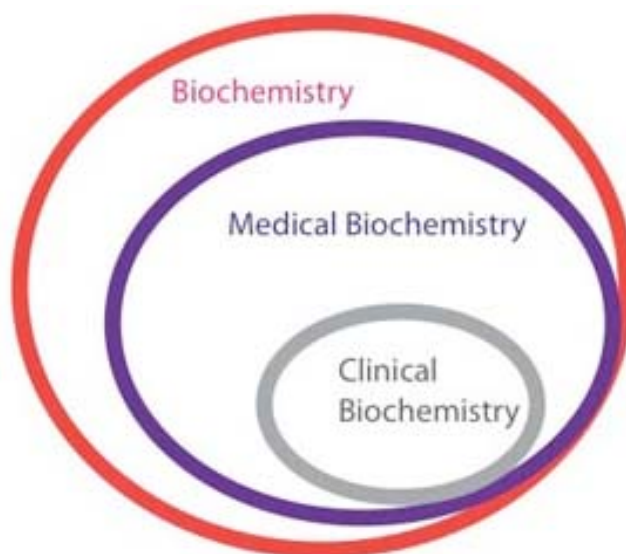


Figure 1. Biochemistry, medical biochemistry and clinical biochemistry.

2. The Scope of Medical Biochemistry

The scope of medical biochemistry, which follows, has been a basis for medical teaching in the discipline, and encompasses most of its current clinical applications. The outline is based on a current textbook intended primarily for medical students (Baynes and Dominiczak 2009). Thus, the typical scope of medical biochemistry includes the following:

The Chemistry of Structures Comprising Human Organism.

The chemical components of the human body: aminoacids and proteins, simple carbohydrates and lipids. Complex carbohydrates and complex lipids. Components of the extracellular matrix. Components of blood and plasma. Biological membranes.

Key Chemical Processes in the Human Body.

The nature of enzymes. Membrane transport mechanisms. Membrane receptors and signal transduction. Oxygen transport. Blood coagulation. The immune response and biochemical mechanisms of hormone action. Structure and function of neurotransmitters. Cellular homoeostasis, growth, differentiation and cancer. The process of ageing.

Nutrition and Metabolism.

Assimilation of nutrients, the function of the gastrointestinal tract, and processes of intestinal absorption. Macro and micronutrients: vitamins and minerals. Bioenergetics and oxidative metabolism. Mitochondrial respiratory chain. Main metabolic pathways: glycolysis, storage and synthesis of carbohydrates, the tricarboxylic acid cycle (Krebs cycle), oxidative metabolism of lipids, and biosynthesis and storage of fatty acids. Biosynthesis of cholesterol and steroids. Lipoproteins and lipid transport. Biosynthesis and degradation of aminoacids. Oxidations and the role of free radicals.

Integrative Aspects of Metabolism:

Glucose homeostasis and the metabolism of body fuels. Calcium and bone metabolism. Nutrition and energy balance. The metabolic role of the liver. Muscle metabolism (its energy metabolism and mechanism of contraction). Water and electrolyte homeostasis and kidney function. The acid-base balance. Note that, historically, the last two topics had been relatively superficially treated in textbooks of biochemistry in spite of their practical relevance.

Elements of Molecular Biology.

Nucleic acids and molecular genetics. DNA, RNA and protein synthesis. Regulation of gene expression. Recombinant DNA technology. Genomics, proteomics and metabolomics.

3. The Changing Scope of Clinical Biochemistry

Clinical biochemistry is driven by the discovery of biomarkers, and the availability of appropriate measurement methods. Therefore, its scope constantly changes. It became an autonomous discipline in the 1940s (see below). Incidentally, the earliest textbook with 'Clinical chemistry' in its title was published in 1883: the *Clinical Chemistry*, by C.H. Ralfe of the London Hospital. In the United States, H.G. Wells (1875-1943), professor of pathology at the University of Chicago published his 'Chemical Pathology' in 1907.

As a discipline, clinical biochemistry includes two main components: methodological and interpretative. The early textbooks were strongly focused on methodology, whereas the majority of contemporary ones emphasize interpretative aspects and clinical correlations, reflecting close professional relationship between clinical chemists and practicing clinicians.

Between the 1950s and 1980s, the focus of clinical biochemistry was on the development of methodologies appropriate for measurement of various analytes in a large number of patient samples, the ways of obtaining biological material, the establishment of normal ranges (reference values), and the principles of quality control in clinical laboratories. Introduction of automated equipment began in the late 1950s.

At that time the range of the offered diagnostic tests included glucose, non-protein nitrogen to assess the renal function, amino-acid nitrogen to gauge the nutritional status, plasma and urinary proteins, lipids, enzymes, electrolytes (including calcium, magnesium and phosphorus), and parameters of acid base balance. Trace metals such as copper and zinc, as well as vitamins, were measured as part of nutritional assessment, and hemoglobin, porphyrins, and iron in the diagnosis of hematological disorders. The measurements of drugs and poisons were being actively developed.

Importantly, for practical purposes, tests within this spectrum were grouped into the 'test profiles' that reflect the function of a specific organ (or a particular - tissue, such as muscle). Organ and tissue profiles were established for liver, pancreas, bone, muscle, heart and kidney. The early profiles had been mostly based on the pattern of organ-

specific enzyme activities. In addition to blood, urine (including urinary calculi), feces, cerebrospinal fluid and other body fluids were examined. Endocrinology-related testing included thyroid function tests, steroid hormones, hormones of hypothalamo-pituitary-adrenal axis, estrogens and progestogens (including assessment of the gonadal, fetal-placental function, and pregnancy), and epinephrine, norepinephrine and related compounds. Before the introduction of radioimmunoassay, which allowed measurement of picogram concentrations of hormones, hormones were measured indirectly (e.g. thyroid hormones were estimated as protein-bound iodine, and steroids, rather crudely, as their urinary metabolites).

A range of 'dynamic' function tests was developed, where a substance (such as, for instance, glucose) is administered first and the response of its plasma concentration monitored for a period of time.

By the late 1970s clinical biochemistry accumulated large interpretative knowledge, reflected in the content of the clinical biochemistry textbooks published at the time. There was an increasing understanding of the concept of biological variability (which is one of the most important contributions of clinical biochemistry to medicine). The investigation of inborn errors of metabolism expanded, and toxicology and drug monitoring became an important part of the clinical laboratory repertoire. Endocrinology became overwhelmingly based on radioimmunoassay and related methods, and similar methodology was being used for tumor marker measurements. Endocrinology and endocrine function tests were fast becoming a major part of clinical biochemistry. Tumor markers and therapeutic drug monitoring became fast-growing areas. The measurement of an increasing number of plasma proteins also remained within the core of clinical chemistry.

Large amount of knowledge generated by clinical biochemistry was now being accepted into clinical practice across medical and surgical disciplines. The practically most important areas were the assessment of water and electrolyte metabolism and hydrogen ion homeostasis, which lead to diagnosis and treatment of an entire range of 'new' clinical disorders. Particularly important was the contribution of clinical chemistry to the diagnosis and monitoring of diabetes (with the introduction of glycated hemoglobin as a measure of time-averaged glycemic control) and the progress in understanding and treatment of diabetic coma (ketoacidosis). The importance of lipids and lipoproteins for public health increased enormously after the results of clinical studies showing the benefit of lipid lowering for cardiovascular risk had been published. Finally, clinical chemistry became important contributor to the development and monitoring of intravenous nutrition. An important methodological development was also the point-of-care testing: development of a range of portable or small desktop analyzers and dry-reagent test strips, which allowed low-volume emergency testing on the hospital wards, or indeed self-testing by patients.

A particularly well-structured textbook of clinical biochemistry has been the Tietz Textbook of Clinical Chemistry where the editors successfully combined the methodological and pathophysiological aspects of clinical chemistry. It was originally edited by N. Tietz, and from 1986 by C.A. Burtis and E.R. Ashwood. In its last (4th) edition, it changed the title to Clinical Biochemistry and Molecular Diagnostics (and

acquired a third editor, D. Bruns), reflecting the fact that clinical biochemistry similarly to general biochemistry, embraced molecular biology.

More recent methodological issues in clinical biochemistry are all associated with high-volume testing: laboratory automation and workflow management, and computational issues. In parallel to expansion of evidence-based medicine, clinical biochemists started to examine systematically the existing evidence for the benefit of diagnostic tests, under the banner of evidence-based clinical biochemistry. There is also fast expansion of molecular diagnostics (in particular the diagnosis of hematological neoplasms), and pharmacogenetics. In recent years, substantial progress has been achieved in genetic screening.

Thus, with an expanding test range, the scope of clinical biochemistry increasingly matches the entirety of 'basic' medical biochemistry. As we have seen above, medical biochemistry also includes elements of immunology and hematology. For historical reasons, in some countries a sort of tribal approach to laboratory medicine persists, and separate clinical laboratories of hematology and immunology exist in addition to clinical biochemistry.

Paediatric clinical biochemistry is an increasingly specialized field, characterized not only by often-different reference values but also by emphasis on diagnosis of inborn errors of metabolism.

4. Natural History of a Scientific Field

As new knowledge is generated, new disciplines emerge in science. They usually form around a cluster of distinct research methodologies. Science creates new knowledge in a particular way, by employing the scientific method based on experimental verification of hypotheses and rigorous validation of results by peer groups (Table 1).

A new field usually emerges from the convergent experimental results of several investigators. Once there is a critical mass of results, a 'new' field is defined, and a complex infrastructure needs to be set up to support its further development, to allow validation of specialist knowledge, and to maintain continuity through teaching and research training. The new knowledge also needs to be disseminated to other disciplines, to develop interdisciplinary research, and to the wider public, to secure political support and funding. These goals are normally achieved through founding of scientific associations, organizing scientific meetings, and establishing specialist journals. Once disciplines mature, their comprehensive descriptions can be found in emerging academic textbooks.

Further, academic progress informs the 'real' life. If the newly generated knowledge has practical dimensions, applications emerge. Such applications may spark development of entire industries and a new manufacturing base (this happened both in the case of molecular biology and clinical chemistry). Finally, scientific fields do not stay static. The scope of knowledge comprising a field changes with time. This may lead to merging or withering of disciplines, and to the appearance of new ones. Naturally it also leads to

particular disciplines coming to the forefront of research for a period – and also, undoubtedly, to scientific ‘fashions’.

Structure of a Scientific Field	
Knowledge Gathering	Investigators Hypotheses Experiments
Knowledge Validation and Dissemination	Journals Scientific Organizations Conferences
Knowledge Maintenance	Textbooks Teaching Training
Practical Applications	Industry / Manufacturing

Table 1. Structure of a scientific field

Underlying all this is a strong academic tradition of personal attribution of scientific discoveries. Therefore, development of any scientific discipline can be traced through the achievements of leading individuals and often through ‘schools’ that form around eminent investigators.

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Biographical Sketch

Marek Dominiczak is Professor of Clinical Biochemistry and Medical Humanities at the University of Glasgow, and consultant clinical biochemist to the National Health Service (NHS Greater Glasgow and Clyde) in the United Kingdom. He graduated from the Medical Academy of Gdansk (now renamed Medical University of Gdansk) in Poland, where he also obtained a doctorate in clinical biochemistry, and (in 2007) habilitation in medicine. He was consultant pathologist to St Luke's Hospital in Malta and lectured biochemistry at the University of Malta in 1980-82. Since 1999 he has also been a docent in laboratory medicine at the University of Turku in Finland.

He published over 100 papers on diabetic complications, the assessment of glycaemic control, atherosclerosis, lipids and cardiovascular prevention. In 1990s he co-ordinated two European projects within the Tempus programs of academic renewal, first one in Poland and second in Estonia.

He is author and editor of books on cardiovascular prevention and general biochemistry. The 'Medical Biochemistry' edited together with J Baynes, now translated into three languages, became a major undergraduate textbook worldwide. For several years Dominiczak also edited the journal *Clinical Chemistry and Laboratory Medicine*.

He founded the Curriculum Development Committee of the IFCC, was a founder member of the Polish College of Laboratory Medicine, and served on councils of the Association of Clinical Biochemists UK, the British Hyperlipidaemia Association, and the Association for Medical Humanities UK. He was also member of the Management Team of the Lipid & Lipoprotein Division of the American Association for Clinical Biochemistry, and has received Outstanding Speaker Awards from that Association. He is also director of the Glasgow Medical Humanities Unit, where he pursues interests in scientific writing, the links and relationships between science and the arts, and the history of laboratory medicine.