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EC4 European Syllabus for Post-Graduate Training in Clinical Chemistry and Laboratory Medicine: version 3 – 2005

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Abstract

The EC4 Syllabus for Postgraduate Training is the basis for the European Register of Specialists in Clinical Chemistry and Laboratory Medicine.

The syllabus:

- Indicates the level of requirements in postgraduate training to harmonise the postgraduate education in the European Union (EU);
- Indicates the level of content of national training programmes to obtain adequate knowledge and experience;
- Is approved by all EU societies for clinical chemistry and laboratory medicine.

The syllabus is not primarily meant to be a training guide, but on the basis of the overview given (common minimal programme), national societies should formulate programmes that indicate where knowledge and experience is needed.

The main points of this programme are:

- Knowledge in biochemistry, haematology, immunology, etc.;
- Pre-analytical conditions;
- Evaluation of results;
- Interpretations (post-analytical phase);
- Laboratory management; and
- Quality insurance management.

The aim of this version of the syllabus is to be in accordance with the Directive of Professional Qualifications published on 30 September 2005.

To prepare the common platforms planned in this directive, the disciplines are divided into four categories:

- General chemistry, encompassing biochemistry, endocrinology, chemical (humoral), immunology, toxicology, and therapeutic drug monitoring;
- Haematology, covering cells, transfusion serology, coagulation, and cellular immunology;

- Microbiology, involving bacteriology, virology, parasitology, and mycology;
- Genetics and IVF.

Keywords: clinical chemistry and laboratory medicine; postgraduate education; professional qualifications; quality.

Introduction

In modern medicine the undeniable value and indispensability of scientific investigations are now universally recognised both for diagnostic purposes and monitoring of disease and in basic epidemiology. The direct treatment of patients is an undeniable task of doctors in medicine. Progress in laboratory science is largely the result of contributions by scientists (general meaning) with an appropriate education and specialisation in the field, i.e., by specialists in clinical chemistry and laboratory medicine[1)]. Clinical laboratory science has developed on a broad front throughout the European Union, resulting in significant differences in what constitutes a national clinical laboratory service in each state. Clinical chemistry is the medical discipline devoted to obtaining, exploring and employing biological knowledge and methods of investigation to obtain knowledge about normal and abnormal biological processes in man. These processes are studied on a general level to obtain an insight into human health and disease, and on a patient-specific level for diagnostic or monitoring purposes. The delineation of clinical chemistry varies from country to country, since there is no sharp boundary to biochemistry, haematology, immunology, microbiology, genetics and the biology of reproductive medicine.

One of the main tasks of the clinical chemist[1)] is the direction and supervision of a laboratory department in a hospital or health service (public or private), where his or her role involves bridging the gap between rapidly developing laboratory science and technology and growing knowledge on the characteristics of disease. He or she must possess fundamental biological knowledge and have the ability to use this knowledge most appropriately as applied to clinical requirements, i.e., diagnosis of disease, and planning and monitoring of therapy. Apart from providing a competent laboratory service, the clinical chemist[1)] must be able to function as a consultant to his or her clinical colleagues and liaise with them in the interpretation of laboratory results. His or her advice and professional consultations have at least three aspects: choosing the most appropriate laboratory investigation in a particular case; ensuring that analyses are performed in the best possible way and correctly reported to provide information; and, most importantly, interpretation of the significance and consequences of the laboratory data obtained (clinical authorisation).

As the results of laboratory investigations and consultations of the clinical chemist[1)] have a direct and important influence on treatment of the patient, it is to the benefit of the public that the profession of the clinical chemist[1)] is duly regulated.

Clinical Chemistry and Laboratory Medicine

Definition

Clinical Chemistry and Laboratory Medicine is a scientific discipline within medicine. It includes the analysis of body fluids, cells and tissues, and interpretation of the results in relation to health and disease.

The exact content of the specialty of clinical chemistry varies considerably from country to country and a modular approach appears essential for suitable integration into the national contexts.

The discipline encompasses fundamental and applied research into the biological and physiological processes of human and animal life, and application of the resulting knowledge and understanding to the diagnosis, treatment and prevention of disease.

Syllabus

This syllabus provides a short description of the profession of clinical chemistry. The name clinical chemist[1)] is used throughout, although it is realised that different names exist in different countries to describe the profession according to the definitions of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

The scope of clinical chemistry is not solely confined to laboratory activities as such, but in daily practice is strongly interrelated with patient care and treatment. Moreover, medical laboratory activities are not purely of a chemical nature, but also involve the practice and study of biochemistry and molecular biology, haematology, immunology, microbiology (bacteriology and virology), parasitology (including mycology), genetics and the biology of reproductive medicine.

This syllabus does not consider the different structures of medical laboratories as developed in their national environments. It is meant to describe the minimum scientific content for professional knowledge and training, appreciating the national authority and responsibility of each member state to organise laboratory medicine within in its own national healthcare system.

Although significant differences exist in the development of clinical chemistry throughout the European Union, in all cases there are some core elements. As well as these core elements, knowledge of biochemistry, haematology, microbiology, parasitology and immunology, genetics and the biology of reproduc-

[1)] Abbreviated in this paper to clinical chemist: i.e., Specialist in Clinical Analysis (polyvalent) or Specialist in Clinical Biochemistry (monovalent) in Spain, Specialist in Medical Biochemistry in Slovenia, Clinical Biologist in Luxembourg or Biologist in France, etc.

tive medicine are necessary in the training of clinical chemists[1)].

Detailed knowledge on the application of chemistry and molecular biology in diagnostic medicine, monitoring of therapy and in pathophysiology is indispensable. Although cytology and medical microbiology are sometimes considered as distinct specialities in laboratory medicine, many mutual interfaces in the investigation of biological samples at the molecular biology level require general knowledge of infectious diseases and medical microbiology, even in the practice of clinical chemistry and immunochemistry. This is even more the case for haematology and immunohaematology; laboratory investigations in haematology are rapidly developing towards molecular biology and instrumental analysis, which are both based on detailed knowledge of basic chemistry and chemical techniques.

There are important physiological, analytical and technical developments in cellular and molecular biology that demonstrate the importance of scientific investigations in the understanding of disease processes, and consequently in the diagnosis and monitoring of disease. Obviously techniques and technology will change, but basic biological and scientific principles will not, and research and development at the scientific level are indispensable for good clinical chemistry.

Quality assurance

Safeguarding and protecting the public against misuse of medical laboratory investigations are important features of good laboratory practice and reliable laboratory diagnostics. Appropriate laboratory management and scientifically based quality assurance procedures must be incorporated into the production and management of data in medical laboratories. These elements of good laboratory practice appear to be increasingly important with the growing possibility of laboratory investigations in medical laboratory sciences.

The clinical chemist[1)]

Training as a clinical chemist[1)] must involve dedicated post-graduate study of at least 4 years, following a comprehensive and appropriate university education of at least 5 years.

Clinical chemists[1)] and specialist medical consultants operate at the same professional level and must use their complementary knowledge to the benefit of the patients and institutions they serve. The complexity and scope of currently obtainable laboratory information inevitably requires professional interpretation of the data obtained.

This interpretation is an essential task of the clinical chemist[1)], for which he should be trained appropriately.

The principal subject of the undergraduate education will usually be chemistry/biochemistry or medicine or pharmacy, but the specific subjects acceptable in a particular member state will vary across the European Union. Post-graduate study should provide an in-depth knowledge of the biology of disease and the procedures and analytical techniques used in a medical laboratory. It is important that there should be a commitment to research and development, which will often be in association with clinical colleagues. The objective is to produce a person competent in laboratory procedures with a sound knowledge of the subject, who is able to interpret and impart laboratory findings and their implications to clinical colleagues. The interpretation of laboratory data is an essential part of the professional task of the clinical chemist[1)], for which he should be trained adequately. The post-graduate study and training must meet national requirements, but in formulating the courses, consideration should be given as to how such requirements might meet those of the European Union as a whole so as not to restrict opportunities for their nationals who might wish to practise in other member states.

European Syllabus

The European Syllabus for post-graduate training in clinical chemistry affords an overview of the fields within the discipline in which the clinical chemist[1)] should be able to demonstrate knowledge and experience with regard to scientific, clinical and management aspects of the subject. This is a programme for knowledge in the field, indicating the level of requirements in post-graduate training in clinical biochemistry, haematology, immunology, microbiology, parasitology, genetics and the biology of reproductive medicine.

The exact content of clinical chemistry varies considerably from country to country. Therefore, the training requirements may best be satisfied by a modular system enabling the clinical chemist[1)] to adjust his or her competence to the demands of the authorities in the host country.

The syllabus is not primarily meant to be a training guide, but on the basis of the overview given, national societies should formulate programmes, indicating what knowledge and experience is needed, appropriate to the national service requirements in different countries.

The breadth of work to be found in clinical chemistry across the whole European Union gives a clear indication that an appropriate description of the field is necessary for all the disciplines.

This general basis is applicable to the whole of laboratory medicine and helps to unify the scientific and clinical principles on which it is based and demonstrates the unity of concepts underlying the diversity of practice (which is more apparent than real). Disease is due to metabolic, genetic, infectious or other disturbances of homeostasis. The study, diagnosis and therapy of disease require clinical chemistry, cell and molecular biology to identify such changes. The classical subdivisions of laboratory medicine are becoming blurred by developments in science and technology, and particularly as a result of the rapid advances in biochemical, cellular and molecular biology. It is essential that the European Syllabus for clin-

ical chemistry should not only recognise its current strength, but should also provide a framework within which all member states can develop their own approaches towards this model. This should facilitate not only the mutual recognition of national syllabuses, but also the maintenance and enhancement of standards of practice.

Syllabus

This syllabus affords an overview of the fields within the discipline in which the clinical chemist[1)] should be able to demonstrate knowledge and experience with regard to scientific, clinical, management and quality assurance aspects of the subject. This is a programme for knowledge in the field, indicating the level of requirements in post-graduate training in clinical biology. This syllabus is not meant to be a training guide, but on the basis of the overview given, national societies should formulate programmes indicating where knowledge and experience is needed appropriate to the national service requirements in the different countries.

Contents

I. Core knowledge

II. Indications for clinical chemistry procedures

1. In the early detection of disease, and in epidemiology.
2. In disease-related diagnosis.
3. In organ-related diagnosis.
4. In monitoring vital functions.
5. In monitoring response to therapy.
6. In the field of drug monitoring.
7. Indications for subsequent specialised examinations.
8. Indications for functional tests.

III. Influence of collection and storage of specimens

1. Place and time of sample collection, preservation, influence of nutrition, drugs, posture, etc.
2. Choice and correct use of anticoagulants and transport media.
3. Care of specimens, identification, transport, storage, influence of temperature, freezing/thawing.

IV. Methodological evaluation of analytical methods

1. Precision and accuracy.
2. Reference methods and statistical comparison of methods (statistical methods to develop).
3. Internal quality assurance and external quality assessment.
4. Analytical specificity and analytical sensitivity.
5. Interfering factors.

V. Case-related medical evaluation of laboratory tests and methods

The clinical chemist[1)] in a consultative role requires a working knowledge of the subject underlying the choice of tests and interpretation of results.

1. Evaluation (recognition of possible fluctuations in comparison to previous values, patterns of abnormalities, extreme values, etc.).
2. Use of reference values: influences of age, sex, way of life, etc., and decision values and limits.
3. Longitudinal evaluation of disease course and therapy monitoring; critical differences.
4. Recognition of combinations of findings typical of diseases.
5. Testing strategies applied to clinical questions.
6. The laboratory report with evaluation of data.
7. Independent performance or suggestions for further investigations.

VI. Clinical training

Training in clinical chemistry requires participation in ward rounds as a member of the clinical team and other contact with the users of the laboratory service, for example, seminars and case discussions.

Study in the following areas will provide a general basic knowledge of clinical chemistry from which consultative skills can be developed.

1. Organ function, anatomy and physiology.
2. Metabolism.
3. Biochemical exploration and testing.
4. Pathophysiology of disease.

VII. Research and development

As laboratory medicine is continually and rapidly evolving, research and development of both the laboratory aspects and their clinical application are indispensable. The clinical chemist[1)] must maintain up-to-date knowledge in all relevant diagnostic procedures. Special attention must be paid to the following:

1. Developments and improvements in methods and techniques; special emphasis on new developments in areas such as molecular biology.
2. Procedures to test and evaluate the steps of a method and the components of an instrument.
3. Evaluation of laboratory-based and clinical research projects.
4. Analyses and documentation of results obtained through research and development, with statistical and scientific presentation of data.
5. Collaborative planning of clinical research based on the liaison function of the clinical chemist[1)] as an essential specialist for interpretation of laboratory data.
6. Publication of papers reporting new or improved laboratory methods and of clinical research papers.

VIII. Laboratory management and quality assurance

1. Laboratory organisation and quality management.
   - Work procedure, work load measurements, emergency laboratory, laboratory planning, selection of equipment and methods, cost-benefit analysis, costing.
2. Quality assessment.
   - Statistical applications in the clinical laboratory: interpretation of statistical laboratory and population data, biological variation, establishment of reference intervals, method comparison.
   - Data management: medical informatics, data processing and telecommunications, presentation and communication of results of investigation (choice of units, design and content of request and report forms).
3. Education of laboratory personnel and writing and maintaining quality procedures.
4. Basic knowledge of clinical epidemiology.
5. Laboratory safety.
   - Handling of potentially infectious samples (e.g., HIV and hepatitis), handling of noxious chemicals and isotopes, mechanical and electrical safety, fire precautions, dealing with an accident.
6. Legal and ethical regulations.
   - Laws, guidelines and recommendations on work in clinical laboratories: in particular, accident prevention and hygiene regulations, handling of isotopes, calibration law, quality control, education regulations, labour laws and occupational diseases.
   - Ethical aspects and conventions on production, interpretation, reporting and use of medical laboratory data.
7. Medical laboratory accreditation.

A. General chemistry, covering biochemistry, endocrinology, chemical (humoral), immunology, toxicology, and therapeutic drug monitoring

Basic knowledge

1. Basic knowledge in chemistry.
   - Homogeneous and heterogeneous systems, distribution and absorption with regard to analytical separation methods. Study of atoms and molecules, especially with regard to stoichiometry and isotope chemical aspects.
   - Knowledge of thermodynamic laws and their application in analysis and biological systems. Reaction kinetics with regard to catalysed reactions and radioactive decay.
2. Basic knowledge in biochemistry.
   - Molecular structure of the body; metabolism, enzymes, metabolites, molecular biology of genetics, biological macromolecules, lipids, hormones.
3. Basic knowledge in medicine.
   - 3.1 Structure and function of the human body, laws on the distribution of substances in the body.
   - 3.2 Human physiology.
   - 3.3 Pathobiochemistry, pathophysiology and pathology.
   - 3.4 Genetics (basic aspects).
4. Basic knowledge of statistics and biostatistics.

Clinical assessment of laboratory analyses

1. Reference intervals and biological variability.
   - Genetic influences, environmental influences, age, sex, nutrition, season and time of day, influence of therapeutic agents.
2. Predictive value of analytical methods, diagnostic sensitivity and specificity.
3. Diagnostic strategies and analytical goals in the use of clinical chemistry tests.

Analytical principles and techniques

1. Separation techniques including gas and liquid chromatography, electrophoresis and dialysis.
2. Standard analytical techniques such as titrimetry and osmometry.
3. Photometric methods: spectrophotometry (UV, visible) atomic absorption, turbidimetry, nephelometry, spectrofluorimetry, flame emission, etc.
4. Spectrometric methods: mass spectrometry, nuclear magnetic resonance, infra-red.
5. Electrochemical techniques: ion-selective electrodes.
6. Techniques for protein analysis and other molecular separation: electrophoresis, chromatography, ultracentrifugation.
7. Techniques for nucleic acid analysis: amplification, investigation of mutations and gene expression.
8. Immunochemical techniques.
   - Immunochemical protein analysis: immunoelectrophoresis, immunofixation, immunonephelometry and turbidimetry.
   - Immunological and other binding analyses using different labels. Homogeneous and non-homogeneous immunoassays.
9. Techniques using radioactive isotopes.
10. Enzyme analyses and substrate determination methods.
11. Knowledge of analytical instrumentation and evaluation of equipment.
12. Knowledge of electronic data processing.

Knowledge and experience in applications in the biochemical, endocrinology, chemical (humoral) immunology, toxicology, and therapeutic drug monitoring fields

1. Carbohydrates.
   - 1.1 Glucose metabolism and regulation.
   - 1.2 Metabolism and regulation of other carbohydrates (e.g., galactose, lactose, glycogen).

1.3 Type 1 and type 2 diabetes mellitus.
1.4 Other hereditary and acquired metabolic disorders (e.g., lactose intolerance, galactosaemia, storage diseases).
1.5 Ketogenesis.

2. Lipids and lipoproteins.
2.1 Metabolism.
2.2 Hereditary and acquired disorders; storage diseases; hypercholesterolaemia; hypo- and hyperlipoproteinaemia; characterisation by classical methodology; apolipoproteins; lipoprotein lipase.

3. Proteins and amino acids.
3.1 Metabolism.
3.2 Important plasma proteins (albumin, immunoglobulin, haptoglobin, transferrin, C-reactive protein, etc.).
3.3 Dysproteinaemia, monoclonal components.
3.4 Tumour-associated proteins.
3.5 Hereditary and acquired disorders of amino acid metabolism.
3.6 Urine proteins and proteinurias.

4. Nucleic acids and purines.
4.1 Metabolism.
4.2 Gout.
4.3 Other hereditary and acquired disorders of purine metabolism.

5. Porphyrins and haem pigments.
5.1 Metabolism.
5.2 Porphyrias.

6. Biogenic amines.
6.1 Metabolism.
6.2 Catecholamines, serotonin and their breakdown products.

7. Water and electrolytes.
7.1 Metabolism.
7.2 Sodium, potassium, chloride abnormalities.
7.3 Oedema and ascites.

8. Acid-base, blood gases.
8.1 Acid-base balance and disorders; buffer systems (bicarbonate, phosphate, protein); Henderson-Hasselbalch equation; acidosis and alkalosis.
8.2 Renal regulation systems.
8.3 Pulmonary gas exchange; oxygen metabolism.

9. Iron metabolism.

10. Vitamins and trace elements.

11. Immune system.
11.1 Functions of the humoral and cellular immune systems and their regulation; cytokines; inflammation; acute phase proteins.
11.2 Surface antigens.
11.3 Hereditary and acquired disorders.
11.4 Immunoglobulin deficiency and overproduction, monoclonal and polyclonal immunopathies.
11.5 Major histocompatibility complex.
11.6 Autoimmune diseases; allergy.
11.7 Complement factors.

12. Enzymes.
12.1 Induction, synthesis and elimination.
12.2 Enzyme patterns in various tissues and body compartments; isoenzymes; diagnostic significance.

13. Cerebrospinal fluid (CSF).
13.1 CSF synthesis and circulation.
13.2 Composition of CSF in comparison to serum.
13.3 Hereditary and acquired disorders of CSF homeostasis.

14. Digestive tract.
14.1 Digestive enzymes in the various sections of the digestive system, including the exocrine functions of the liver and pancreas.
14.2 Hydrochloric acid, bicarbonate and bile secretion.
14.3 Fluid and electrolyte secretion.
14.4 Absorption.
14.5 Gastrointestinal hormones.
14.6 Hereditary and acquired disorders of the digestive system.
14.7 Malabsorption, including vitamin malabsorption.

15. Exocrine functions of the pancreas.
15.1 Acute pancreatitis.
15.2 Chronic pancreatitis.

16. Liver and biliary tract.
16.1 Physiology; normal and disturbed functions of the liver; metabolism, synthesis, biotransformation, excretion.
16.2 Enterohepatic circulation; metabolism of bilirubin and bile acids.
16.3 Hepatitis, cirrhosis, cholestasis, necrosis.

17. Kidneys and urinary tract.
17.1 Physiology; normal and disturbed renal function.
17.2 Excretory substances in the plasma and urine; glomerular filtration rate and clearance; activity and effects of diuretics; free water clearance.
17.3 Proteinuria.
17.4 Acute and chronic renal insufficiency, nephritis, nephrotic syndrome.

18. Heart and circulatory system.
18.1 Normal and disturbed circulation.
18.2 Myocardial infarction and shock; enzyme patterns and marker proteins; fluid balance.
18.3 Hypertension.
18.4 Heart failure, blood markers.

19. Skeletal and locomotor system.
19.1 Function and metabolism of muscles, bones, cartilage, synovial and connective tissues (fasciae, tendons).
19.2 Hereditary and acquired disorders, especially of calcium and phosphate metabolism, vitamin D, collagen and proteopolysaccharide metabolism.

20. Endocrine system.
20.1 Physiology, biosynthesis and catabolism of hormones.
20.2 Hormonal regulation, hormone transport, receptor systems.

20.3 Functional disorders of the thyroid gland, the parathyroid glands, the adrenal cortex, the adrenal medulla, the endocrine part of the pancreas, the gonads, the placenta, and the pituitary-hypothalamus system.

21. Pregnancy, perinatal laboratory analysis.
    - 21.1 Hormone analyses; in vitro fertilisation.
    - 21.2 Molecular biology of hereditary disorders.
    - 21.3 Inherited metabolic disease.
22. Drug monitoring.
    - 22.1 Pharmokinetics, pharmacodynamics and bioavailability of drugs, pharmacogenetics.
    - 22.2 Therapeutic range.
    - 22.3 Individual determinations for the most important drugs: digoxin, theophylline, anticonvulsants, immunosuppressants.
23. Poisoning.
    - 23.1 Pathomechanisms of the most important types of poisoning.
    - 23.2 Knowledge of the preparation and preservation of specimens, regulations for examination, documentation of examinations, chain of custody.
    - 23.3 Knowledge of strategies for group recognition of poisons by extraction, isolation and identification.
    - 23.4 Individual determinations for the most important types of poisoning, e.g., ethyl alcohol, carbon monoxide, barbiturates, benzodiazepines, tricyclic antidepressants, methaemoglobin, methyl alcohol, ethylene glycol, benzene, toluene, etc.; cholinesterase in the case of organic phosphate intoxications.
    - 23.5 Tests for drugs of abuse.
    - 23.6 Radioactive isotope toxicology.
    - 23.7 Toxicology: LSD, entactogenic drugs, opiates, cannabis, cocaine.
    - 23.8 Professional and environmental toxicology.
24. Molecular biology investigations of non-infectious diseases.
    - 24.1 Prenatal diagnosis of inborn errors of metabolism.
    - 24.2 Oncogenes.

B. Haematology, including cells, transfusion serology, coagulation, and cellular immunology

Basic haematology

1. General morphology and blood cell counting.
    - 1.1 Determination of erythrocyte sedimentation rate; determination of haemoglobin concentration, haematocrit, cell counts and knowledge of haematological parameters (MCV, MCH, MCHC, RDW).
    - 1.2 Preparation and staining of blood smears, with microscopy evaluation.
    - 1.3 Investigation of haemolysis.
    - 1.4 Flow cytometry and leukocyte sub-grouping.
2. General haemostasis.
    - 2.1 Coagulation tests.
    - 2.2 Determination of coagulation factors; control of anticoagulation factors, supervision of all treatments.
    - 2.3 Investigation of fibrinolysis.
    - 2.4 Determination of antithrombin III and heparin.
3. Immunohaematology.
    - 3.1 Blood group typing, ABO and Rh(D); D-variant determination, Kell.
    - 3.2 Detection of irregular antibodies.
    - 3.3 Cross-matching of blood samples for transfusion; indirect antiglobin test, direct antiglobin test.
    - 3.4 Rhesus and ABO antagonism.
4. Haematological biochemistry of erythrocytes.
    - 4.1 Detection and measurement of variant and minor (HbA_2 and HbF) haemoglobins.
    - 4.2 Red blood cell enzymes.
5. Theoretical and clinical background.
    - 5.1 Haemoglobinopathies and thalassemias.
    - 5.2 Vitamin B_{12} and folic acid deficiencies; iron status.
    - 5.3 Kinetics of blood cells and platelets.
    - 5.4 Enzymology of blood cells and platelets.
    - 5.5 Haematooncological abnormalities (leukaemias, lymphomas, polycythaemias).
    - 5.6 Possible causes and background of anaemias.
    - 5.7 Immunological determination of coagulation factors and knowledge of coagulation abnormalities (factor deficiency, increased fibrinolytic activity) and regulation and monitoring of thrombosis and disseminated intravascular coagulation; use of anticoagulant drugs.
    - 5.8 Blood group antigens and other antigen systems as considered in blood transfusion (including genetics); selection criteria for donors for blood transfusion; several types of transfusion reactions.
    - 5.9 Medical applications, clinical relevance and indications for the administration of blood and blood components.
    - 5.10 Haematopoiesis and haemostasis physiology.

Extended haematology

1. Morphology and haematopoiesis.
    - 1.1 Morphological investigation of bone marrow smears, including different staining procedures; PAS staining for intracellular glycogen; Sudan black staining for lipids; iron staining; acid phosphatase; esterase and peroxidase staining.
    - 1.2 Investigation of cellular characteristics and abnormalities by flow cytometry.
    - 1.3 Haemoglobinopathies; haemoglobin electrophoresis on cellulose acetate, in agar gel; Kleihauer test.

1.4 Investigation of anaemias, both congenital and acquired; Ham test and sucrose test.
1.5 Detection of abnormal haemoglobin derivatives: spectrophotometric analysis.
1.6 Haemato-oncology.
1.7 Myelodysplasia.
1.8 Ganglion exploration.
1.9 Lymphoid system pathology.

2. Haemostasis.
2.1 Investigation of platelet function; influence on platelet aggregation by ADP-adrenaline, collagen, ristocetin, ADP, ATP; determination of serotonin; spontaneous aggregation; clot retraction; platelet factor III determination, glass pearl test.
2.2 Use of chromogenic substrates for the determination of coagulation factors.
2.3 Detection of circulating inhibitors, thrombo test diluted curve, cephalin dilution curve.
2.4 Protein S, protein C.
2.5 Theoretical background and clinical background and knowledge of the following subjects: prekallikrein, high molecular kininogen determination, plasminogen, antiplasmin, plasminogen activators.

3. Immunohaematology and blood banking.
3.1 Typing of irregular (auto) antibodies; determination of antibody titre.
3.2 Extended blood group typing (beyond ABO, Rhesus D and Kell).
3.3 Investigation of transfusion reactions.
3.4 Preparation and application of blood components.
3.5 Organisation of blood banking.
3.6 Typing of B and T lymphocytes.
3.7 Platelet antibodies.
3.8 Typing of leukocytes and tissue antigens.
3.9 Recognition of cell markers using monoclonal antibodies.
3.10 The application of plasmapheresis, both in donors and in patients.

C. Microbiology, covering bacteriology, virology, parasitology, and mycology

1. General aspects.
The investigation of biological samples in infectious diseases is different from the other specialities in that it requires general knowledge of pathogenic agents (bacteria or viruses) and of host reaction.
1.1 Definition of infection and infectious disease: natural bacteriological ecosystem.
1.2 Pathogenicity of bacteria and viruses; disinfection.
1.3 General epidemiology of infection and infectious diseases.

2. Diagnostic procedures.
2.1 Specimen selection and collection (blood, urine, sputum, faeces, others).
2.2 Specimen processing: smears, staining, cultures including cell cultures, susceptibility testing, antigen detection.
2.3 Usual techniques for microbe and virus identification (including principal differential characteristics).
2.4 Molecular biology techniques for characterisation of microbes and viral agents.
2.5 Bacteriological and viral serology.

3. Bacteria and viruses.
Succinct description of responsible bacteria and viruses in bacteriological and viral syndromes or diseases (including principal differential characteristics).
3.1 Bacteria: *Neisseria gonorrhoeae* and *N. meningitidis*, *Staphylococcus aureus*, *Streptococcus pyogenes* (especially *S. agalactiae* and *S. pneumoniae*), *Escherichia coli*, *Salmonella*, *Shigella* and other Enterobacteriaceae, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Clostridium perfringens*, *C. tetani*, *Bacteroides* spp, *Listeria monocytogenes*, *Legionella*, *Mycobacterium tuberculosis* and others, *Treponema pallidum*, *Chlamydiae*, *Mycoplasma*, etc.
3.2 Viruses: herpes (herpes simplex, herpes varicellae, cytomegalovirus, Epstein Barr virus); hepatitis A, B, C, D, E; human immunodeficiency virus; enteroviruses (poliovirus); rubella, mumps, measles, parvovirus B19, RSV, myxovirus, rhinovirus, coronavirus, adenovirus, rotavirus, papillomavirus, rabies, etc.

4. Bacteriological and viral syndromes or diseases: epidemiology, main clinical signs, basis for biological diagnosis, treatment.
4.1 Meninged syndrome.
4.2 Septicaemic syndrome.
4.3 Urinary and genital infections.
4.4 Bacteriological and viral diarrhoeas.
4.5 Respiratory infections.
4.6 Human acquired immunodeficiency syndrome.
4.7 Sexually transmitted diseases.
4.8 Hepatic virus infections.
4.9 Cytomegalovirus infections.

5. Antibiotics and antiviral agents
5.1 Basic knowledge of antibiotics and antimicrobiological therapy.
5.2 Antibiotic and antiviral sensitivity test.
5.3 Antibiotic and antiviral resistant mechanisms.

Medical parasitology (including mycology)

1. Epidemiology, main clinical signs, basis for biological diagnosis (including a succinct description of parasites and fungi without biochemical characteristics), treatment.

1.1 Amoebiasis: *Entamoeba histolytica*.
1.2 Giardiasis, cryptosporidiosis and uro-genital trichomoniases.
1.3 Malaria.
1.4 Toxoplasmosis.
1.5 Intestinal, hepatic and urinary helminthiasis: strongyloidiasis, ancylostomiasis, enterobiasis, ascariasis, schistosomiasis (*Schistosoma mansoni* and *S. haematobium*), fascioliasis (*Fasciola hepatica*) and taeniasis (*Taenia saginata*).
1.6 Fungal infections (*Candida albicans*, *Cryptococcus neoformans*, etc.).
1.7 Aspergillus infections (*Aspergillus fumigatus*).
1.8 Dermatophyte infections (*Microsporum canis*, *Epidermophyton floccosum*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*).
1.9 Leishmaniosis.
1.10 Echinococcosis.
1.11 Pneumocystosis.
1.12 Filariosis.

2. Usual techniques for parasite and fungus identification.
3. Immunological and molecular diagnosis of parasitic and mycological diseases.

D. Genetics and IVF

Biological genetics includes cytogenetics and molecular genetics.

1. Cytogenetics

At the end of his training, the clinical chemist[1)] must be able to appreciate the relevance of the prescription, evaluate the cohesiveness of the results, and to perform and supervise the realisation of a karyotype and an in situ hybridisation.

1.1 Karyotype:
- To know the different analysable materials and the culture requirements.
- To know the culture conditions according to the sample and indications (medium, support, culture time).
- To perform chromosomal preparations as directed.
- To master acquisition of the principal types of chromosomal bands.
- To perform high-resolution karyotypes (replication bands).
- To perform microscopic examination, display capture on analyser and karyotype classification.
- To know how to supervise and critically analyse the quality of the chromosomal preparations and the resolution level of the chromosomal bands.
- To appreciate the validity criteria of chromosomal analysis.

1.2 Molecular cytogenetics:
- To know how to perform in situ hybridisation fluorescent techniques: centromeric probe, chromosome painting probe, specific probe of a locus on metaphase or interphase.
- To acquire the necessary knowledge to perform comparative genomic hybridisation on microarrays.
- To appreciate the validity criteria of molecular cytogenetics assays.

1.3 To be able to describe the analysis strategy for the abnormalities listed below and to recognise their diagnostic, prognosis and/or therapeutic interest:
- Chromosome number abnormalities.
- Mosaicism.
- Structure abnormalities in equilibrium and disequilibrium.
- Chromosomal microrearrangement.
- Identification of a chromosomal marker.
- Identification of chromosomal variants.
- Chromosome fragility and chromosome breakage syndromes.

2. Molecular genetics

At the end of his training, the clinical chemist must be able to appreciate the prescription relevance, evaluate the cohesiveness of the results, perform and supervise the carrying out of, molecular genetics analysis.

2.1 Molecular genetics procedures:
- To perform the different procedures of nucleic acid extraction (genomic DNA, RNA, RNA polyA+).
- To perform the different identification methods for point mutations.
- To perform the different identification methods for genomic mutations.
- To perform the different methods of study of DNA polymorphisms (SNP, microsatellites).
- To perform the different methods of gene expression study at the RNA level.
- To acquire the necessary principles to perform and interpret DNA and cDNA microarray techniques.
- To appreciate the validity criteria for molecular genetics analysis.

2.2 To be able to describe the analysis strategy of the following pathological types and to recognise their diagnostic, prognosis and/or therapeutic interest:
- Monogenic disorders (autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant).
- Oligo- and polygenic disorders.
- Mitochondrial disorders.

3. Reproductive medicine

Basic knowledge

- Sperm count and morphology.
- Huner test and in vitro penetration.
- Antisperm antibodies.
- Sperm selection test.

Extended knowledge

1. IVF
   - Sperm preparation for fertilisation with frozen sperm or from testicular biopsy.
   - Fertilisation by the ICSI technique.
   - Embryo culture.
   - Embryo preparation for transfer.
2. Freezing
   - Sperm and embryo freezing.
   - Cryopreservation of gametes and embryos.

Examples of scientific and medical literature

1. Textbooks

Note: As new editions of textbooks appear regularly the following list only serves as an example and is certainly not exhaustive; frequent updating is necessary.

1.1 Burtis CA, Ashwood ER, editors, and Tietz NW. Tietz textbook of clinical chemistry. Philadelphia, PA: WB Saunders Company, 1998.
1.2 Greiling H, Gressner AM, editors. Lehrbuch der Klinischen Chemie und Pathobiochemie. 3. Auflage. Stuttgart: FK Schattauer Verlag, 1995.
1.3 Thomas L, editor. Clinical laboratory diagnostics. Frankfurt am Main: T-H Books, 1998.
1.4 Johnstone A, Thorpe R, editors. Immunochemistry in practice. Oxford: Blackwell Scientific Inc, 1996.
1.5 Rose BD, Post T, Narins R. Clinical physiology of acid-base and electrolyte disorders. New York: McGraw-Hill Book Company, 1994.
1.6 Greenspan FS, Strewler GJ, editors. Basic & clinical endocrinology. Los Altos, CA: Appleton & Lange Medical Publications, 1997.
1.7 Felig P, Baxter JD, Frohman LA, editors. Endocrinology and metabolism. New York: McGraw-Hill Book Company, 1995.
1.8 Sackett DL, Haynes RB, Tugwell P, editors. Clinical epidemiology, a basic science for clinical medicine. Boston, MA: Little, Brown and Company, 1991.
1.9 Stites DP, Terr AI, Parslow TG, editors. Medical immunology. London: Appleton & Lange, 1997.
1.10 Friedman RB, Young DS, editors. Effects of disease on clinical laboratory tests. Washington, DC: AACC Press, 1997.
1.11 Young DS, editor. Effects of drugs on clinical laboratory tests. Washington, DC: AACC Press, 1995.
1.12 Young DS, editor. Effects of preanalytical variables on clinical laboratory tests. Washington, DC: AACC Press, 1993.
1.13 Richard-Lee GL, Foerster J, Lukens J, Wintrobe MM, editors. Wintrobe's clinical haematology. Philadelphia, PA: Lea and Febiger, 1998.
1.14 Dacie JV, Lewis SM. Practical haematology. London: Churchill Livingstone, 1995.
1.15 Spivak JL, Eichner ER. The fundamentals of clinical hematology. Cambridge: Harper and Row Publishers, 1993.
1.16 Bloom AL, Forbes CD, Thomas DD. Haemostasis and thrombosis. London: Churchill Livingstone, 1994.
1.17 Engelfriet CP, Contreras M, Mollison PL. Blood transfusion in clinical medicine. Oxford: Blackwell Science Inc, 1997.
1.18 Babior BM, Stossel TP. Haematology: ''a pathophysiological approach''. New York: Churchill Livingstone, 1994.
1.19 Hall R, Malia RG, editors. Medical laboratory haematology. London: Butterworths, 1991.
1.20 Colman RW, Hirsh J, Marder VJ, Salzman EW, editors. Hemostasis and thrombosis; basic principles and clinical practice. Philadelphia, PA: JB Lippincott Company, 1994.
1.21 Stiene-Martin EA, Lotspeich-Steininger ChA, Koepke JA, editors. Clinical hematology: principles, procedures, correlations. Philadelphia, PA: JB Lippincott Company, 1998.
1.22 Harmening DM, editor. Clinical hematology and fundamentals of hemostasis. Philadelphia, PA: FA Davies Company, 1996.
1.23 Hoffbrand AV, Petit JE. Essential haematology, Oxford: Blackwell Scientific Publications, 1993.
1.24 Adelberg EA, Jawetz E, Melnick JL. Review of medical microbiology. Los Altos, CA: Lange Medical Publications, 1993.
1.25 Murray PR, Baron EJ, Pfaller MA, editors. Manual of clinical microbiology. Washington, DC: American Society for Microbiology, 1999.
1.26 Bangert SK, Marshall WJ, editors. Clinical biochemistry: metabolic and clinical aspects. London: Churchill Livingstone, 1995.

2. Scientific and medical journals

2.1 Annals of Clinical Biochemistry.
2.2 Antimicrobial Agents and Chemotherapy.
2.3 British Medical Journal.
2.4 Clinical Chemistry.
2.5 Clinical Chemistry and Laboratory Medicine.
2.6 Clinica Chimica Acta.
2.7 Current Advances in Clinical Chemistry.
2.8 Current Contents.
2.9 European Journal of Clinical Microbiology and Infectious Diseases.
2.10 Journal of Biological Chemistry.

2.11 Journal of Clinical Endocrinology and Metabolism.
2.12 Journal of Clinical Microbiology.
2.13 Nature.
2.14 New England Journal of Medicine.
2.15 Scandinavian Journal of Clinical & Laboratory Investigation.
2.16 Science.
2.17 The Lancet.

3. Primary literature

It must be stressed that reading primary literature (articles, surveys, etc.) is of utmost importance to keep informed on the ''state of the art'' in clinical biology. For this reason, students should adopt a system for themselves of keeping constantly informed on developments in the field of laboratory medicine and related subjects.