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Review

Medical immunology: Two-way bridge connecting bench and bedside

Ger T. Rijkers[a,b,*], Jan G.M.C. Damoiseaux[c], Herbert Hooijkaas[d]

[a] Science Department, University College Roosevelt, PO Box 94, 4330 AB Middelburg, The Netherlands
[b] Laboratory for Medical Microbiology and Immunology, St. Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, The Netherlands
[c] Unit Cellular Diagnostics and Cell Therapy, Central Diagnostic Laboratory, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, The Netherlands
[d] Unit Medical Immunology, Department of Immunology, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands

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ABSTRACT

Medical immunology in The Netherlands is a laboratory specialism dealing with immunological analyses as well as pre- and post-analytical consultation to clinicians (clinical immunologists and other specialists) involved in patients with immune mediated diseases. The scope of medical immunology includes immunodeficiencies, autoimmune diseases, allergy, transfusion and transplantation immunology, and lymphoproliferative disorders plus the monitoring of these patients. The training, professional criteria, quality control of procedures and laboratories is well organized. As examples of the bridge function of medical immunology between laboratory (bench) and patient (bedside) the contribution of medical immunologists to diagnosis and treatment of primary immunodeficiency diseases (in particular: humoral immunodeficiencies) as well as autoantibodies (anti-citrullinated proteins in rheumatoid arthritis) are given.

1. Introduction

Medical immunology is a specialization within the field of immunology which encompasses the clinical laboratory practice for allergy, autoimmunity, immunodeficiency, lymphoproliferative disorders, and transfusion and transplantation immunology. In the Netherlands the medical immunologist is the laboratory specialist responsible for adequate immunological analyses in a clinical laboratory. This also includes pre- and post-analytic consultation. The medical immunologists are united in the *College of Medical Immunologists* (CMI). The mission of the CMI is "to advance the quality and application of novel insights and methods in the daily practice of the laboratory for clinical immunology".

In the current manuscript we first describe the past, the present and the future of the medical immunology in the Netherlands. Next, we give two examples, one in the area of primary immunodeficiency and the other in the area of autoimmune diseases, where medical immunology has benefitted clearly from the close collaboration between basic and clinical research in the Netherlands. The transplantation immunology will be discussed by Tilanus et al. [1; this issue].

2. Medical immunology in the Netherlands: past, present, future

For a long time, the term *immunity* was more or less synonymous with antibodies. Insight into the structural and functional aspects of cellular immunity began only after 1960. It gave a boost to the development of clinical immunology as a discipline within health care. From that moment onwards it became possible to rationally analyze derangements of the immune system and of mechanisms of reactivity toward micro-organisms, autoantigens, allergens, malignant cells and transplanted tissues and organs. At the same time, diagnostic modalities were vastly extended and refined. Beginning in 1970 immunology received a tremendous impulse from the developments in molecular biology, biotechnology, genetics and computer science [2,3].

Nowadays, immunology has established its natural place in the field of health care [4,5]. The International Union of Immunological Societies (IUIS) provided a definition of clinical immunology: "Clinical immunology is a clinical and laboratory discipline dealing with the study, diagnosis and management of patients with diseases or

* Corresponding author at: Science Department, University College Roosevelt, PO Box 94, 4330 AB Middelburg, The Netherlands. Tel.: +31 118 655500; fax: +31 118 655508.
E-mail addresses: g.rijkers@ucr.nl, g.rijkers@antoniusziekenhuis.nl (G.T. Rijkers), jan.damoiseaux@mumc.nl (J.G.M.C. Damoiseaux), h.hooijkaas@erasmusmc.nl (H. Hooijkaas).

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disease processes resulting from disordered immunological mechanisms, and conditions in which immunological manipulations form an important part of therapy and/or prevention" [6]. Immunological disease may have both adult and pediatric presentations. While it is recognized that many immunologists will have responsibilities in both clinical and laboratory areas, the extent of their responsibilities in the different areas will vary. Many immunologists will work entirely in the laboratory [6].

Clinical immunology in the Netherlands is a profession of medical doctors (MD's). This is the "bedside part" of clinical immunology (see also review on Clinical Immunology elsewhere in this issue [7]). The term used in the Netherlands for the healthcare directed laboratory-based discipline is medical immunology. As such the medical immunologist is a laboratory specialist, PhD or MD/PhD, responsible for adequate immunological analyses and giving pre- and post analytical advice to clinicians involved in immunological patients. The scope of medical immunology includes immunodeficiencies, autoimmune diseases, allergy, transfusion and transplantation immunology, and lymphoproliferative disorders including the monitoring of these patients as well as monitoring of immune modulating therapies. Close interactions between the clinicians and the medical immunology laboratory is essential for optimal functioning of both specialties; symbiosis is the biological term for this type of interaction. For immunologists who want to become involved in these diagnostics and associated research activities a special training in immunology in health care is needed. It is clear that many clinical disciplines such as rheumatology, neurology, dermatology, pediatrics, internal medicine, etc. will profit from the services of both clinical and medical immunologist.

A formally and adequately trained medical immunologist is able to (a) Deal with all the laboratory aspects of diagnostic investigations; (b) will have a broad knowledge of both basic aspects of immunology and the pathophysiology of immunological disturbances and hypersensitivity in humans; (c) serves as a professional partner to the clinicians who deal with patients with disorders in which the immune system is involved and (d) acts as a lookout to identify, evaluate and translate new (potential) developments in the field of diagnostics and immunotherapy.

Expertise in medical immunology must promote the quality of immunological investigations in the service of health care. This comprises the adequate quality assurance of the technical aspects of tests, professional training of technical personnel, assessment of sense and nonsense of diagnostic requests and interpretation of results. In this setting, medical immunologists have their own place in the community of laboratory based specialists along, but distinct from clinical chemists, medical microbiologists and pathologists.

Immunology has historically always been a scientific discipline strongly represented in the Netherlands. Most universities have always harbored multiple groups working in immunology. The Dutch Society for Immunology (Nederlandse Vereniging voor Immunologie, NVVI) is the scientific guild of the Dutch immunologists. As early as 1974 the NVVI established a formal scientific training for immunological investigators. In 1978 the Concilium Immunologicum was constituted, which had a dual authority: (1) The official acknowledgment of investigators with a well-established knowledge of, and experience with, immunological research. (2) The additional registration as medical immunologist, if the experience and actual occupation of the candidate, concerned the application of immunology to health care. The formal requirements for training in medical immunology were established in 1987 [8]. Medical immunologists work in health care laboratories, most of them in academic centers (Fig. 1). Currently (August 2014), 47 medical immunologists are active in The Netherlands, while an additional 9 are in training.

The training program in medical immunology [8–10] is focused on the acquisition of the specific knowledge and experience required to carry out immunological laboratory diagnostic tests for the benefit of patient care in a responsible way and to manage a laboratory with this task. To perform this task adequately, during the training program the trainee must acquire broad and thorough knowledge concerning the pathophysiology of the immune system. In consultation with the relevant medical specialists, the trainee must also become familiar with all aspects of immunological laboratory diagnostic tests and with the evaluation of requests for tests and of the results obtained, against the background of other clinical and laboratory findings. In order to function adequately in a hospital laboratory setting both organizationally and in conjunction with colleagues, it is a must that during the training program the trainee also acquires sufficient knowledge of other laboratory disciplines. Finally, the trainee must acquire knowledge and experience of laboratory management in all its aspects according to ISO 15189 (a set of particular rules and requirements for quality and competence which also specifies the quality management system requirements for medical laboratories).

The NVVI has set up a Training and Registration Committee (COR) to monitor and regulate this program, including registration and re-registration. The quality of the training centers is assessed by the Visitation and Accreditation Committee (CVA) in collaboration with the COR. These two committees are coordinated by the College of Medical Immunologists (CMI) of the Dutch Society for Immunology. The COR acts on behalf of the NVVI and is answerable to them.

In the hospital, the medical immunologists functions as a laboratory specialist, as other specialists in laboratory medicine such as clinical chemists. Both at the national as well as European level, several activities have been initiated, which still are ongoing, to formalize the status of medical immunology as Laboratory Medicine and harmonization between diagnostic laboratories [11,12]. The organizations involved are the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), the Union Européenne de Médicins Specialistes (UEMS), Section of Laboratory Medicine/Medical Biopathology [13], the Federation of Laboratory Specialisms (FMLS). This harmonization process takes time and effort because the profession of laboratory medicine differs between countries within the EU in many respects. In a study [13] many differences between the 28 countries of the EU were identified: predominantly medical or scientific professionals; a broad or limited professional field of interest; inclusion of patient treatment; formal or absent recognition; a regulated or absent formal training program; general or minor application of a quality system based on ISO norms. The harmonization of the postgraduate training of both clinical chemists and of laboratory physicians has been a goal for many years. It is an important challenge to harmonize professions and difficult choices will need to be made. This is closely related to the principle of free movement of people, a cornerstone of European integration. This policy translates to equivalence of standards and harmonization of the training curriculum, both the central tasks of the European professional organizations. The need for a single European name has been recognized and addressed by EFLM. It was agreed upon the name Specialist in Laboratory Medicine as it encompasses all specialists working in the field from whatever academic background and whether polyvalent or subspecialized [14].

The future will bring new challenges and opportunities. Imaginative and innovative solutions to current problems and new questions will arise. The necessity for continuous funding of (fundamental) immunological research which applies to various (overlapping) immune mediated diseases is an example of both a challenge as well as opportunity. Adventure, rewards and pleasure will be there for those who are prepared and are fortunate enough to have the resources to participate in Laboratory Medicine [15].