25 Years of "LaboratoriumsMedizin" and Progress in Laboratory Medicine

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LaboratoriumsMedizin celebrates its 25th birthday this year. Since 1977 the world of laboratory medicine and clinical diagnostics has witnessed a period of enormous progress and development. Frequently, however, the people who spend their professional careers in the clinical laboratory are so caught up in the pressures of day-to-day operational requirements that it is difficult for them to stand back enough to get a broader perspective and to appreciate fully the extent of the changes that have taken place in the profession. Trying not to be distracted by too much detail of the innovations introduced into the clinical laboratory over the past 25 years, I think that three major achievements stand out:

New laboratory tests and techniques

Many new diagnostic techniques and laboratory tests have been introduced into the clinical laboratory. The number of test parameters that can be requested and carried out even in the routine clinical laboratory (not to speak of specialised laboratories) has increased enormously as a result of both research on the fundamental pathogenesis of diseases and the development of new methods in themselves. The two Nobel prizes awarded respectively to the inventions of monoclonal antibodies (Koehler and Milstein, 1984) and the polymerase chain reaction, PCR (Kary Mullis, 1993), are only the more visible tips of a huge iceberg of innovation in the field. Without these techniques, many immunoassays and methods of molecular genetic testing that are currently taken for granted would simply have been impossible. These and other techniques have been applied to nearly every clinical field. Thus, the efficient and early diagnosis of heart diseases has been considerably improved through increasing use of markers such as troponins and brain natriuretic peptide, BNP. In the field of cancer, methods such as prostate specific antigen testing and immunotyping of leukemias have been increasingly used, just as sensitive TSH and free hormone assays in many endocrine diseases. In inflammation and infection, testing for analytes such as C-reactive protein, procalcitonin, antigens and nucleic acids of infectious pathogens, etc., has been introduced. Several completely new areas of laboratory diagnostics have been opened up and introduced into the routine clinical laboratory, such as drug monitoring, the molecular diagnostics of genetic and infectious diseases, or immunophenotyping of blood cells. In some cases new tests had to be developed and introduced under tremendous time pressure as the result of the emergence of new diseases or urgent clinical demands. Examples of these are in the diagnostics of HIV or hepatitis C infection, as well as the monitoring of novel immunosuppressive drugs or the assessment of (designer) drug consumption.

Automation and informatics

Automation and electronic data management have been vital in the increase of the productivity and efficacy of the clinical laboratory. The clinical importance of the role of the clinical laboratory is also highlighted by the large numbers of tests per parameter which can nowadays be carried out within relatively short time intervals. This has only been made possible by a high degree of automation and the introduction of electronic data management. Automated and online random access analysis have become standard for many clinical chemistry, coagulation, haematology and immunoassay parameters. Many laboratories and clinics or practices communicate orders and reports through the use of electronic laboratory and clinic information systems. In the late 1970s, a pure clinical chemistry laboratory of a university hospital with a limited spectrum of parameters generated aproximately 10,000 test results per technician per year. 25 years later, at the beginning of the 21st century, a central university hospital laboratory with a much broader range of automated and non-automated methods releases 100,000 test results per technician per year. Not only has productivity been increased, but automation has also led to great improvements in the actual analytical quality of laboratory testing itself. By combining productivity and quality, laboratory automation has become an indispensable tool capable of dealing with the quick turn-around-times increasingly demanded in modern high tech-medicine. However, the very success of automation is itself a potential threat to the clinical laboratory. There are several reasons for this. Firstly, many clinicians have an overly-simple "black-box" impression of the clinical lab and are openly questioning the need for laboratory physicians or clinical chemists as professional academic leaders in the clinical lab. Secondly, automation facilitates point-of-care testing, which of course is indispensable in many emergency and intensive care situations. The number of point-of-care-test parameters is steadily increasing. However in many cases, this increase is not due to an attempt to handle vital emergency situations or to solve problems of sample stability (which are valid reasons for point-of-care testing in "classical" cases such as blood gas analysis) but merely for reasons of the convenience of near patient testing. Sometimes novel parameters are even introduced as point-of-care applications before traditional clinical laboratory test formats. In the light

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of this trend and particularly in view of recent progress in chip technology, many specialists are beginning to wonder whether, sooner or later, the clinical laboratory will be replaced by a lab-on-a-chip.

Standardization and quality control

Rigorous quality control systems were developed to guarantee the validity of the test results. Since laboratory diagnostics plays a vital role in identifying and confirming clinical diagnoses and monitoring the course of diseases, the validity of each laboratory test is of course of utmost importance. This means that test results must be independent of the test site, reproducible and accurate. To achieve this apparently obvious objective, the performance and calibration of methods have had to be standardized, and standardized procedures for internal and external quality control systems have had to be introduced into the clinical laboratory. For many parameters, international reference methods and/or reference materials have been established. National guidelines have been released which recommend or even impose the frequency of quality control measurements as well as acceptable limits of imprecision and inaccuracy for the measurement of many parameters. Until recently, it was widely accepted that the precision and accuracy of test results could be guaranteed through the simple testing of quality control material and/or pooled specimens. Nowadays, industrial standards of accreditation and certification are increasingly being applied to the clinical laboratory. These are aimed at controlling not only the outcome of laboratory testing but also the actual process of carrying out the test. Thus, quality control has been formalised to be much more than a matter of individual responsibility and standards of a lab director. This new approach significantly improves the quality of the test results. Such formalisation of quality control is also needed for *in vitro* diagnostics carried out using near-patient test devices. For this reason, several national and international societies of clinical chemistry or laboratory medicine correctly recommend that quality control of point-of care-testing should be coordinated and supervised by a professional laboratory expert.

Looking ahead

A 25th anniversary is a time not only to look back but also ahead. What are the risks to and opportunities for the clinical laboratory? What are the future demands on the clinical laboratory likely to be? In the present era of "Molecular Medicine", laboratory medicine has no reason to fear the future, even if some parts of in vitro diagnostics will inevitably leave the laboratory to be performed instead at the bedside, in the doctor's office or even at the patient's home. The sequencing of the human genome and the elucidation of new pathogenetic networks is already providing a rich source of novel laboratory parameters. Chip-, laser- and nanotechnology provide new technical platforms that can be adapted to both traditional and new test parameters. A lot of expectation is being generated by molecular testing. On a purely technical basis, such testing can already be carried out in the clinical laboratory but it still lacks a broad clinical application. To date the most frequent indication of nucleic acid analytics is in the diagnosis of infections rather than that of genetic diseases. At first sight this is surprising in view of the strong genetic component of many common diseases such as atherosclerosis, diabetes mellitus or cancer. However, many genes and polymorphisms have to be identified and validated in epidemiological studies before they can be introduced into routine clinical diagnostics and prognostics. Because the majority of these diseases are polygenic and polyallelic in origin it is obvious that genetic laboratory diagnostics will be multiparametric. For example, uniparametric genotyping of polymorphisms in the genes for Factor V, HFE and apoE are not helpful in the diagnostics of individual patients, despite their statistically significant association with venous thromboembolism, hemochromatosis and Alzheimer's disease, respectively. For the assessment of individual disease risks these parameters need to be integrated into a broader genotypic and also phenotypic test panel. Great progress has been made in solving the technical issues of multiparametric genotyping and phenotyping. The big problem for the future is how to adequately convey into the clinical setting the complex information generated by multiparametric analyses. This will probably require a paradigm shift in at least a part of laboratory practises. In the past the clinician requested specific parameters to be tested in order to confirm or rule out a clinical diagnosis. In many cases the laboratory specialist and the doctor interpreted the outcome of such analyses in a one-dimensional system by comparing the test results to reference or ideal values. In contrast multiparametric testing will need the use of algorithms, cluster analyses or neural networks to convert large amounts of data into practical clinical diagnoses and therapeutic decisions. The requirement for the clinical lab to provide not only the data but also an interpretation of the data also applies to expression analysis at either the RNA level (transcriptomics) or the protein level (proteomics) as well as for the multiparametric analysis of small molecules by tandem mass spectrometry (metabolomics).

The number of testable parameters is exploding at the same time as the financial resources in the public health system are becoming more and more tight. In this situation, the clinical laboratory expert must be able not only to guarantee the analytical quality of test results and provide a broad spectrum of test parameters but must also manage the economics of the laboratory and establish cost-effective diagnostic strategies.

Thus the future will continue to bring more and more changes as novel tests, novel technologies and novel demands are introduced. To keep up with these rapid changes, systematic continuous (medical) education of both laboratory professionals and clinicians will be needed. Therefore our journal, LaboratoriumsMedizin, will continue to have an important role to play in this aspect.

This editorial has also been published in Clinical Laboratory International on the occasion of this journal's 25th anniversary.