Thoughts about the future of clinical chemistry

by
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A considerable number factors are affect the development of clinical chemistry. Some of them open up fascinating possibilities, some pose a threat to the profession. I would like to mainly discuss some of the bothersome trends.

The need for cost containment forces laboratories to streamline their procedures. This is a natural continuous process, but it has in some cases led to impaired quality. This especially concerns some immunoassays and especially steroid assays. One example is determination of cortisol in urine. We have switched from immunoassay to HPLC and recently to LC-MS because immunoassay, whether done directly or after extraction, gives unacceptable results (1, 2). Vitamin D is a similar problematic assay (3), and the recent article on testosterone in female serum in Clinical Chemistry by Taieb et al. may represent the most serious problem (4). These are only some examples, there are serious problems with many other assays, e.g., estradiol in serum from prepubertal girls. I do not know of a single commercial method that is good enough for that purpose. We maintain RIA methods for several steroid hormones (e.g. estradiol and testosterone) comprising extraction and chromatography, but they are more expensive than the direct methods, and only pediatricians use them regularly. It is hard to get the message through.

How have we come to this situation? I think a crucial aspect is that most of those who nowadays are responsible form immunoassays have no experience of the problems involved in assay development. Commercial companies utilize this and sell useless methods to naïve customers. The methods may have been compared with earlier methods giving acceptable correlation. However, that may concern only high values. However, even when the laboratorian is aware of the weakness of a method, he/she cannot afford buying a better analyzer or doing the assay manually. And the clinician will detect the difference only after several years, if ever. I think that we cannot afford this development. Skilled clinicians detect the difference and switch to better methods, which may consist of imaging – an adrenal tumor can be diagnosed by imaging techniques rather than by a hormone assay. However, this is not the most important argument, the most important aspect is that we must not accept bad work. What we do should must serve the intended clinical use. We cannot determine every steroid hormone by mass spectrometry (many we can and should do), but we should not do determinations that are inadequate.

Can we change the situation? I am certain that we can by improving standardization, quality assessment schemes, accreditation and method approval. However, presently only part of these are effective, but they can be developed. I think that we need to be much more tough with accreditation of laboratories and approval of commercial methods. In the USA, FDA is tough, but they still do not control some of the most essential quality problems, and I am afraid that they are not even aware of them. However, assay standardization is the basis for improved quality, and as I have discussed in some articles,

this is a task that cannot be solve with the resources presently available (5). It is obvious that we have to keep the cost for improving quality on a level that corresponds to the clinical value achieved. At the moment we spend too little on quality. However, how much should be spend is hard to calculate because the clinicians pay for bad quality, not the laboratory (6).

Unfortunately, standardization and quality control are fairly dull, and therefore it is not easy to attract innovative people to work with these subjects although much more needs to be done. Based my own experience of standardization, there are innovative people who feel responsibility for the methods that they have developed and are willing to do much work to ascertain that their methods are used correctly. However, this work is badly under budgeted and there are ongoing projects for only a few of the assays that need to be standardized. When available standardization needs to be implemented and at the moment we may only wish that assay manufacturers do that. I think that we need tools to enforce it. At the moment we do not have that.

The problems with impairing standard of some assays is partially a result of the increasing use of automation. However, the effect of automation is mostly positive, faster turnaround times, lower costs, better precision and in many cases also better overall quality. However, it may also separate the laboratory from the clinic and the laboratorian from the clinician. I see this as a problem. I would like to see myself as a participant in the diagnostic process, not as an "engineer'' pushing the button of an automatic robot. If this happens, we may be replaced by robots or the whole department of clinical chemistry can be outsourced to an outside company. This has been done to a variable extent in some countries, in Sweden this trend was popular 5-10 years ago but there it has changed. In Finland a similar trend is now popular (we usually follow Sweden with a 5-10 years delay and do the same mistakes and include a few new ones caused by translation errors). Presently, out laboratory is transformed into a separate company, which it is still owned by the hospital district. It is going to be an interesting experiment.

I think that it is important that the laboratory is an integral part of the hospital and health care system. Otherwise the interests of the hospital and the laboratory may be conflicting. This is a typical example: We can reduce costs by centralizing most assays from several surrounding units. However, especially in outpatient wards this causes increased costs because of delays in laboratory results. Eventually this will lead to increased use of point-of-care (POC) methods, which may be outside control of the laboratory. While I believe in increased use of POC, I think that the laboratory should retain control in order to assure quality.

One of the main reasons why I wish to keep the laboratory as an integral part of the hospital is that I think that we need to more actively participate in the diagnostic process. This can be done by participating in clinical meetings and rounds on the wards. However, still more important will be to develop diagnostic algorithms that help the clinician to interpret laboratory data more efficiently. We now often produce more than 20 new

laboratory results every day for each patient and, when we combine this with all other diagnostic information, e.g., imaging, pathology, serology and microbial assays, we provide the clinician with such a vast amount of information, that it is impossible to interpret efficiently even by an experienced clinician with a well developed "personal neural network". We started to work with neural networks after developing methods for assays of various forms of PSA. When the clinicians asked what the combined effect of certain combinations of total and free PSA meant, I had to admit that I did not know, and therefore we started to develop algorithms for this. I was amazed to see the results and it is obvious that this kind of interpretation is much more accurate if a computer does this with a well trained neural network (not over trained) than when a human being does it (7). Urologist to whom I have showed our algorithms are enthusiastic when I demonstrate then, but very few use them. Thus, we have not yet found methods applicable to practical clinical use. I suspect that we need to introduce this approach in the education of medical students. This may be eventually be successful when the "joystick generation" starts studying medicine, but I will not give up trying to find methods that are acceptable to the present generation of MDs.

I can easily identify numerous problems that diagnostic algorithms would cope with better than conventional clinical methods (and there are a lot networks already available, although few are in clinical use). We just need to start working on them. Obviously this requires close collaboration with clinicians, and this I think is important in everything we do. It is now very easy to do research in clinical chemistry – new techniques offer unlimited possibilities to develop better diagnostic methods. It is easy to get engaged in genomics, biotechnology and proteomics and these are so interesting that we do not actually need any hospitals or patients to do good research, cell lines and mice actually much more easy to control than patients. However, just because of this I think that we every day have to remind ourselves of the fact that we are clinical chemists.

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