Host: This is the podcast from *Clinical Chemistry.* I am Bob Barrett.

The past two decades have seen phenomenal investment in microtechnology in the biological sciences. In the April issue of *Clinical Chemistry* five experts in the field of microtechnology answered questions about the scope of the technology and how it could impact the clinical laboratory.

Our guest in this podcast, Dr. Peter Wilding, an Advisory Member of the Center for Biomedical Micro and Nanotechnology, an Emeritus Professor of Pathology and Laboratory Medicine, and Former Director of Clinical Chemistry at the University of Pennsylvania Medical Center, continues their conversation.

So tell us, Dr. Wilding, what exactly is microtechnology, and how long has it been utilized in the clinical laboratory?

Dr. Peter Wilding: Well, microtechnology is any technology that employs micro-sized components, micro-sized volumes, dimensions, etcetera. It's a technology which has been and is still very attractive to developers because of the real and the potential advantages that derive from these features. And one of the most formidable of these features is the ability to control fluid transport at the micro-volume level.

Now, microtechnology has been used for a long time in clinical labs, in the form of valves and tubing, ion-specific electrodes, microparticles employed in devices for immunoassay, such as latex agglutination, and increasingly now in the area of molecular pathology.

Now, you mentioned the length of time that this has been used, and it's interesting that over 25 years ago, the Technicon Corporation marketed an analyzer, which was derived from the famous Smack, that involved many micro-type features and used sample volumes of only one microliter.

So microtechnology is certainly not new in the clinical laboratory, and today, well, we see a widespread use of MicroWell titer plates, with up to a 1,000 wells per plate, and there are micro-arrays with thousands of distinct locations on just one array.

But to prepare, to address, and to react with these distinct locations requires microtechnology for dispensing sub-microliter volumes to these locations.

So essentially, the technology is broad in its application and it’s been with us for quite a time.

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Host: The current buzzword seems to be “nanotechnology.” Isn't it a step backwards to be considering microtechnology?

Dr. Peter Wilding: No, no. The interesting thing about this is, the two terms are now starting to be used interchangeably. And the reason is that they are so frequently used together.

By definition, the physical dimension of nanostructures are those that have features less than one micron. And we are well aware of the advantages of microtechnology, but at the same time, we have got to be willing to accept the limitations.

One can definitely go too small for particular applications. And the problem with nanosystems is in controlling factors such as surface chemistry. As devices become smaller, the ratio of the sample and the various analytes in it, to the surface area or to the surface area that the sampling turns to, tends to increase markedly.

An example, if one has a reaction vessel which holds say 200 microliters, then one would usually anticipate that it would have a surface area to volume ratio of approximately 1:2 square milometers per microliter. But when you come down to the use of microchips that hold just 10 microliters, that ratio can climb to over 20. So there are factors which cause real problems employing nanotechnology in many way.

Also the issue of sampling and having a representative sample always has to be considered. Most current assays in the clinical laboratory use samples in the 2:100 microliter range.

So if you reduce the sample volume or the reaction volume down to nanoliters, picoliters, or even femtoliters, this can create significant problems for constituents which exist at the really low concentrations.

And also, if one is attempting to isolate rare or low incidence cells from blood, one may need to process over 10 milliliters of sample just to find sufficient cells. You can see that the applications of nanotechnology in this situation are really limited. But again, I would emphasize that we tend to use both nano and microtechnology in concert with each other.

Host: How do these new technologies differ from what's currently in use, and how do these systems benefit laboratorians and even the general public?

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Dr. Peter Wilding: Well, as I stated before, microtechnology can be really good at controlling low volume fluid flow. So numerous clinical analyzers in use today employ valves, metering devices, and small capillary flow systems. And in many of the point-of-care testing devices that we use, there are dimensions in the micron range. Some of them employ submicron or if you like nanoparticles as adsorbents and as a medium to carry antibodies.

And this type of application, the point-of-care application, highlights the specific benefits of markedly increasing surface area in reactive situations and demonstrates really how micro and nano can be used simultaneously.

However, I would point out that, with the exception of the use of microparticles or submicron particles, beads, whatever, the number of viable applications for nanotechnology in the clinical laboratory today is still very limited.

Host: Well, it seems microtechnology is quite useful to people working in labs. So why isn't the use of these systems more widespread?

Dr. Peter Wilding: I truly believe that most laboratory scientists fail to understand just how much microtechnology is already employed in the clinical labs and elsewhere.

But one has got to be cognizant of the barriers that delay greater penetration into the clinical lab workplace. The most obvious ones are the failure to develop devices that compete with current systems, from the point of view of cost and convenience. Where we have seen significant inroads of course is in the field of point-of-care testing, where convenience is essential and some higher costs can often be tolerated.

And I think we are going to discuss the success stories such as point-of-care testing later, but I would say that there has been a resistance from many healthcare workers at the point-of-care to add the role of analyst to their job when they know that there is a well-equipped laboratory in the building or at hand.

And only when the speed of assay is paramount and the technology is convenient do these people tend to embrace point-of-care testing.

One sees this beautifully with glucose testing, which is very convenient, it's very low cost, and nurses do this all the time.

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But other areas, we are starting to see significant inroads into areas such as emergency medicine, etcetera for cardiac testing. But this is going to grow, but it's still not really widespread.

Host: What exactly are some of the factors that may have delayed progress in the field, and really in your opinion, is the development actually slow compared with other industries?

Dr. Peter Wilding: Well, I would point out that microelectronics took three to four decades to reach its current state, if one looks at the iPod or the BlackBerry. And I really believe that there will be an increasing number of applications over the next few years.

There are numerous biotechnology companies, both large ones and small ones, that are addressing the application of this technology to point-of-care testing, for analyte such as troponin, thyroid-stimulating hormone, etcetera.

But again, we have to keep remembering that there are tens and millions of glucose analyzers being used at the bedside and at home, all of which can be classified as microtechnology.

And I think as the discipline of molecular biology grows rapidly, then we are going to see an expanding repertoire of tests, which will use microtechnology in that area.

Now, a lot of those tests require nucleic acid or DNA or RNA amplification or need to isolate and manipulate small numbers or individual cells. And microtechnology comes into its own when one looks at DNA or nucleic acid amplification and cell isolation or cell manipulation. So it's a new technology, but it's coming, and it's going to enter the clinical laboratory in large number of areas in a relatively short time.

Host: Well, you mentioned success stories, what about those stories for the technologies that are experiencing widespread use?

Dr. Peter Wilding: Well, I already mentioned the success of the devices for glucose at the point-of-care, but there are hundreds of devices being sold around the world for other applications, such as drug screening, urine analysis, coagulation, cardiac assessment, virus detection, for example HIV, and all of these really employ microtechnology.

They often use immunoassay as the detection medium and all sorts of varying types of technology for demonstrating the result. But they are all really in the micro level.

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But there are also some very successful applications not always associated with the clinical lab, such as accelerometers, which are found in every modern automobile. And these of course represent the classic example of the success of microtechnology.

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But there is also in the clinical laboratory devices such as the Agilent Bioanalyzer, that's one of the fully integrated systems. And this particular system, which will do DNA, RNA, or protein sizing, based on capillary electrophoresis, is a fully integrated system using small microchips, which carryout capillary electrophoresis. And to do that without microtechnology is almost inconceivable.

But at the same time, we have also seen tremendous success of the use of microtechnology in biomedical research and in drug development. In the pharmaceutical industry, the screening of thousands of compounds as candidates for drugs, for new drugs, is now solely based on microtechnology.

And at the same time, the tedious task of carrying out so-called "patch clamping," which is the way electrophysiologists test the effect of new drugs on isolated cells, that particular technique, patch clamping, is an application which is absolutely required for the FDA on all new drugs.

And if one does this by the use of microtechnology, it can be done faster and more reliably than we ever thought possible. And so there are numerous success stories which are around.

Host: What about other industries, how might they be changed by incorporating microtechnology applications, for instance, point-of-care testing?

Dr. Peter Wilding: I mentioned before that point-of-care devices incorporate micro-dimensions, but then they do this either with their flow channels, their valve, or fluid metering systems. And the i-STAT analyzer, which was first launched way back in 1992, is a classic example where microtechnology incorporates these features. And that particular analyzer is now available to perform, I think, with approximately a 12 or a dozen or more analytes.

So there is one in which the microtechnology has actually been incorporated into point-of-care testing very successfully.

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Now, what the new generations of point-of-care devices are attempting to do is to match, improve on, or for the speed and convenience of assays that the i-STAT does. But what they are trying hard to do is to reduce the cost to a point where the use of the point-of-care device becomes preferable or at least a viable alternative to the central laboratory. And the i-STAT system, because of its cost, made limited inroads into the clinical laboratory.

Now, what I didn't mention is the nature of the materials which are being used to create microtechnology systems. In the early systems, many of them involved micro-fabricated components made from silicon. Today, we have got infinitely more flexible approach, which allows for the use of other materials, such as plastic, polymer, carbon fibers, paper, and micro and nano beads made from a huge number of compounds.

So this new flexible approach will ultimately result, in my opinion, in a variety of choices that will end in products that really satisfy the economic needs, the sensitivity requirements, and above all the convenience factors demanded by the technologists, the nurse, the patient, and the doctor, etcetera.

Host: Well, conversely, are there other industries that are exploring microtechnology applications whose developments could benefit clinical applications; one example could be biowarfare detection devices?

Dr. Peter Wilding: Well, my response to this is that the advances in molecular biology and molecular pathology, which I mentioned earlier, really do have significant applications in biowarfare, for example, for monitoring biohazard, detecting infections, detecting airborne pathogens, etcetera.

And some specialized devices are already being constructed for pathogen identification using immunological and nucleic acid amplification systems. And there are several companies that have devoted their effort toward satisfying the needs of the Defense Department.

In general, because these applications are less sensitive to cost issues, the products are not destined for the clinical lab in their early forms, but the overlap in need will in my opinion inevitably benefit both uses.

And there is a robust product. And there have been several available to carryout PCR in small handheld devices, and one of the first was produced by the Cepheid Corporation for specific used by military personnel in war zones.

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So other industries are gaining from clinical applications, but where we will inevitably also gain from the applications being developed for agencies such as the Defense Department.

Host: Dr. Peter Wilding is an Advisory Member of the Center for Biomedical Micro and Nanotechnology, an Emeritus Professor of Pathology and Laboratory Medicine, and Former Director of Clinical Chemistry at the University of Pennsylvania Medical Center. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 15 Minutes.

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