Technological Frontiers in Laboratory Practice

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Abstract: In an effort to stimulate both discussion at this meeting and actual development efforts in the future, this presentation will address clinical laboratory processes where advances in technology can make a significant impact. A matrix chart will be used to consider processes which are common to laboratories ranging in scope from point-of-care to commercial operations. Clinical laboratory processes from specimen collection through result reporting and specimen storage, retrieval, and disposal will be considered for potential improvement by the application of both current and emerging technologies.

Clearly robotics (and automation in general) is now being applied to many specimen and reagent manipulations in traditional clinical laboratories. We will consider whether any of this technology is useful in the point-of-care setting: in the physician office laboratory; in a hospital satellite laboratory. The analogy between robotics and unitized test systems for point-of-care and physician office laboratories will be explored in order to find other areas where technologies such as micro-fluidics might be applied.

Non-evasive technology, if it can be commercialized successfully, has the potential for changing the order-collect-process-analyze-report paradigm to one of the order-analyze-report. The advantages seem obvious; cost-effectiveness is the issue.

Advances in computing and communications will affect all types of clinical laboratory operations. Finding areas where these advances will be able to optimize laboratory practice is an opportunity for everyone involved in the clinical laboratory industry. We will discuss areas where industry and laboratorians might work together to achieve laboratory practice improvements.

I am pleased to have been invited to challenge you to advance the practice of clinical laboratory science. My presentation this afternoon will provide examples of how new and emerging technologies can be useful in advancing clinical laboratory practice. I will use some examples to show, using a matrix format, how specific technologies can impact specific clinical laboratory practices in different laboratory arenas (Figure 1). Over the course of the next forty minutes or so, I would like us to consider where technology can have a significant impact when applied to these clinical laboratory processes. If you will, please keep this matrix in front of you and as technologies are presented and ideas occur, note those areas where you think we can get more "bang for our buck." I'll not touch on every current or emerging technology. I am providing only some examples. As you can see, the matrix shows processes on the left column and five laboratory practice arenas across the top. Where these processes and laboratory arenas meet are cells of the matrix depicting a specific process at work in a

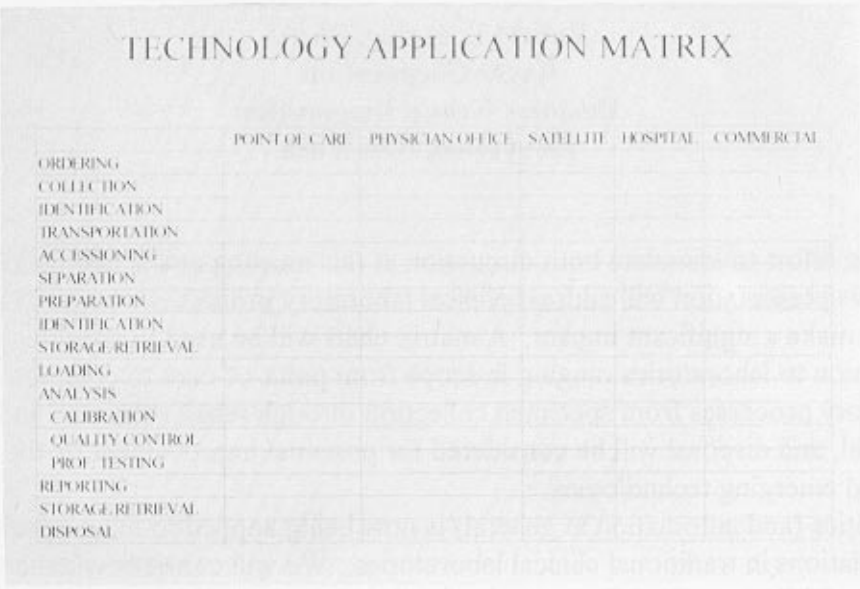


Figure 1. Impact of technology of specific clinical laboratory practices.

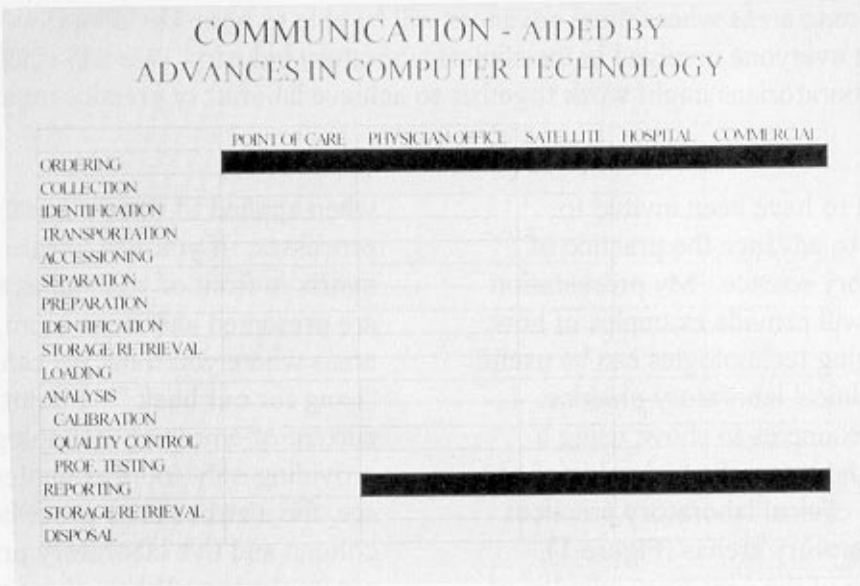


Figure 2. Computer technology.

particular laboratory setting. I will show several slides with multiple cells highlighted to show those areas of the matrix where a selected technology could have a positive impact.

My objective here today is twofold: To encourage you to (1) identify what technologies I've not covered, and (2) determine where those I have covered show the most promise. Over the next few days you will be working together in various workshops where what we are doing now may prove useful, may perhaps kindle your own creativity in thinking about technology applications and how they might improve laboratory processes. The profession and business of clinical laboratory practice will be advanced further if even just a few seeds are germinated here today.

First, let's talk about communication, and advances made possible by the explosive growth of computer technology (Figure 2). I figure progress is being made in the areas of test ordering in all of the laboratory arenas because an order for laboratory work, inpatient or not, is generally the same. So you see, I've highlighted in blue all of the laboratory arenas in the ordering process row. For reporting, I think most improvement will be possible in the physician office lab and in the inpatient setting for satellite and hospital laboratories. Not really well depicted here is the fact that all patient settings will be affected for reporting from work done by commercial laboratories.
I want to digress momentarily to demonstrate the use of the matrix in a way that lets you see how you may also use it over the next few days. Sometimes a completely new paradigm is needed to make a significant impact on processes. For many decades, all of us in the clinical laboratory have been working with centrifuges to pack cells at the bottom of our glass or plastic tubes. We even added gunk to settle between the packed clots and serum. We've used plastic beads and other barriers to help harvest the maximum amount of serum or plasma from each tube. Still, we always pack the unneeded material at the bottom of the tube. With the help of a paradigm shift, DuPont developed an axial separation technology where cells in a serum tube are packed against the glass tube by axial spinning creating the centrifugal force. With a specially developed plastic tube, air probe, sensor, and separation seal, the process can harvest serum quickly in a device which occupies only a small space. The result is a tube which can be used to provide aliquots for analysis, be placed on our automated instrument directly, and can also store the serum for later use.

So now I will show you the modified matrix with some highlighted areas for the axial separation technology application (Figure 3). As you can see, I have manually highlighted the separation process row in the lab arenas of satellite, hospital and commercial operations. Now back to the communication story. Why will communication aided by advances in computer technology make an impact? Well, let us look at some aspects of integrated chip technology which have changed dramatically over the past fifteen years. By the way, many of the slides I will use today to illustrate the technology applications have been loaned to me for this presentation. These next few I borrowed from Dr. Carl Burtis of the Oak Ridge National Laboratory, an expert on technology and its application in clinical laboratory science. Here we can see the amazing, explosive growth made over fifteen years in the speed and equivalent transistor number, while the

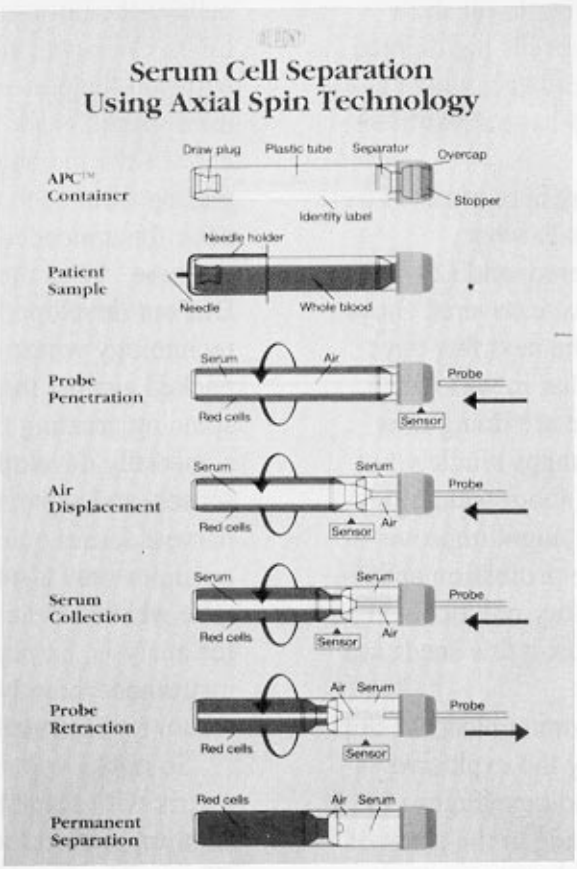
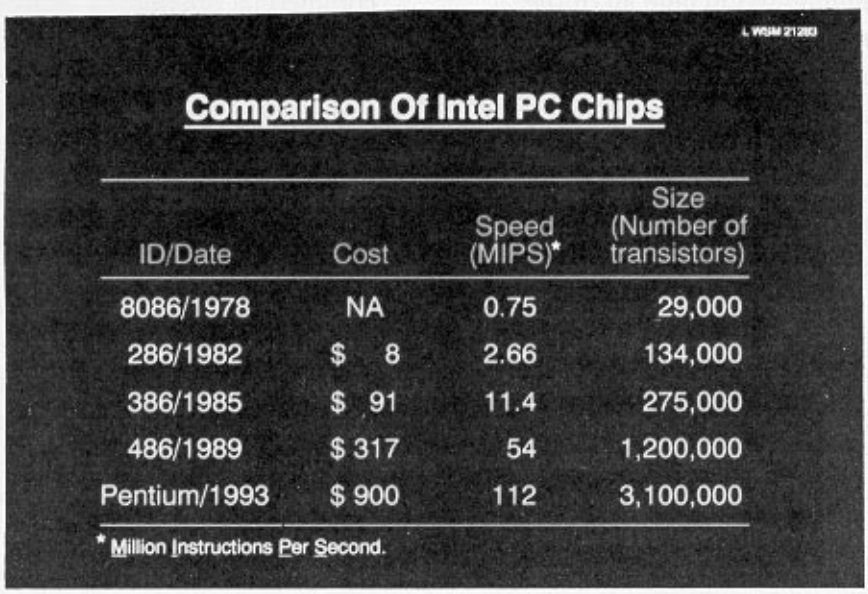


Figure 3. Axial separation technology.



Comparison Of Intel PC Chips

ID/Date	Cost	Speed (MIPS)*	Size (Number of transistors)
8086/1978	NA	0.75	29,000
286/1982	$ 8	2.66	134,000
386/1985	$ 91	11.4	275,000
486/1989	$ 317	54	1,200,000
Pentium/1993	$ 900	112	3,100,000

* Million Instructions Per Second.

Figure 4. Comparison of Intel PC Chips. (Source: Dr. Carl Burtis, Oak Ridge National Laboratory)

cost has only increased about a factor of ten (Figure 4). In the June 1995 issue of Clinical Biochemistry, Burtis writes: "The minimum feature size of an individual transistor on the Pentium chip is about ½ of a micron, which is astonishingly small when compared with a human hair, whose diameter is about 50 microns. In 1965, Gordon Moore, a cofounder of Intel, predicted that the transistor density of integrated chips (ICs) would double every two years. As you can see, this prediction continues to be amazingly accurate, and by extrapolation, by the year 2000, computer chips are expected to be available that contain from 50 to 100 million transistors per chip and that are capable of executing over 2 billion instructions per second."[1] Smaller, faster, and less expensive computer chips make a device such as this personal communicator from AT&T a reasonable tool for physicians to transmit orders and to receive results from wherever they happen to be. With the computer and built-in cellular phone and using e-mail for communicating, we can see why someone has declared that we are moving from the "information age" into the "communication age." The effectiveness of this communication technology will allow physicians to communicate with either a hospital or laboratory information system to place orders or retrieve results no matter where the physician is located.

We all know how microprocessors have been integrated into the current array of laboratory instruments from point-of-care, hand-held devices to the large sophisticated analyzers used in hospital and commercial laboratories. That technology does not need attention in this presentation. However, an area not even on the matrix should be mentioned here. Namely, clinical laboratory management and the education of clinical laboratorians by sophisticated PCS with multimedia capabilities. Another quote from Burtis: "Because of their relative low cost and high memory capacity, the widespread availability of vastly improved operating systems and application software packages for use with them, PCS and workstations have become indispensable tools in the everyday management and operation of the clinical laboratory." As a management tool, the PC allows the laboratory professional to manage and optimize the logistics of specimen, data, and staff flow within the laboratories to monitor and tract the financial aspects of the laboratory; and to organize and maintain the documentation needed to comply with burgeoning governmental regulations. In addition, the PC and its peripheral components are fast becoming essential tools for the training and education of all levels of laboratory staff. With the addition of CD-ROM technology and multimedia software to the PC, systems are now available that have audio, video, and graphics capabilities with unlimited educational potential. These communication applications are really just common business and education tools being brought into the clinical laboratory.

Now let's look at another technology which has analogies with computer integrated circuit manufacturing. I'll call this general area microtechnology and will suggest that it has applicability in three of the laboratory processes of our matrix: sample collection, plasma/serum separation from cells, and of course, analysis. By microtechnology in general, I mean the miniaturization of devices used in the analytical process. These miniaturized devices require far less plasma or serum sample, or better yet, can use whole blood, which is why their effect is also felt in the

sample collection and separation processes. How do they get there? The disciplines of biotechnology and solid-state physics, when combined with advances in the material, computer, engineering, and manufacturing sciences, all provide new measurement technologies which lead to new clinical laboratory applications. The parts and modules of yesterday's large automated chemical analyzers are being reduced to a micro scale and integrated to produce individual devices, sensors. Even hand-held chemical analyzers can be made when microelectronics are combined with these other technologies.

This miniaturization process uses microchips, microelectronics, microcomponents, and microsensors to make it possible to create point-of-care analyzers which are hand-held and useable by health care workers who are not professional laboratorians. In the movement toward system improvement, innovators have moved the technology from separate methods, reagents, and hardware (the modular approach) to integrating these modules into one system. Early examples of this first step into integration were the Kodak Ektachem 700 in the large analyzer class and the Kodak DT 60 physician office laboratory analyzer. Both these Kodak developments merged the method and the reagent onto a dry chemistry slide. More recently, the integration of modules and miniaturization have both been applied to create the I-Stat point-of-care analyzer. It combines the use of whole blood, and a disposable reagent sensor package to create a hand-held device which is capable of producing results for most of the analytes frequently requested on a STAT basis in an inpatient setting. An example of this miniaturization is the I-Stat reagent pack which can draw up a whole blood specimen from a finger stick. This certainly qualifies the system as a miniaturized chemical analyzer.

Still further into the ever-expanding arena of multiple analytes from a whole blood specimen run at the point-of-care is the Abaxis system. After collection, by skin puncture, this system uses capillary action to load whole blood into the rotor, which is pre-loaded with its reagents. The Abaxis system can produce profiles of tests for metabolic diagnosis, cardiac or liver profiles and drug testing. A rotor uses the presence of microchannels to distribute the whole blood sample to the designated reaction chambers. This technology combines microelectronics, advanced optics molded into the rotor, high precision molding, microfluidics to move the blood and a disposable, unit dose, dry-reagent rotor to integrate the sample, reaction, and measurement cell.

I also want to point out here that this micro, unit dose-type technology brings with it some other operational advantages. Maclin and Mahoney in the Journal of Clinical Ligand Assay[2] pointed out that reduced control testing is possible for the following reasons:

a) Solid state, stable reagents
b) More precise molding and manufacturing techniques
c) In process manufacturing controls
d) Microcomputers
e) Electronic calibration
f) Instrument self-monitoring and self-adjustment
g) Instrument checks/error messages for wide variety of sample, reagent, and instrument problems
h) Electrodes

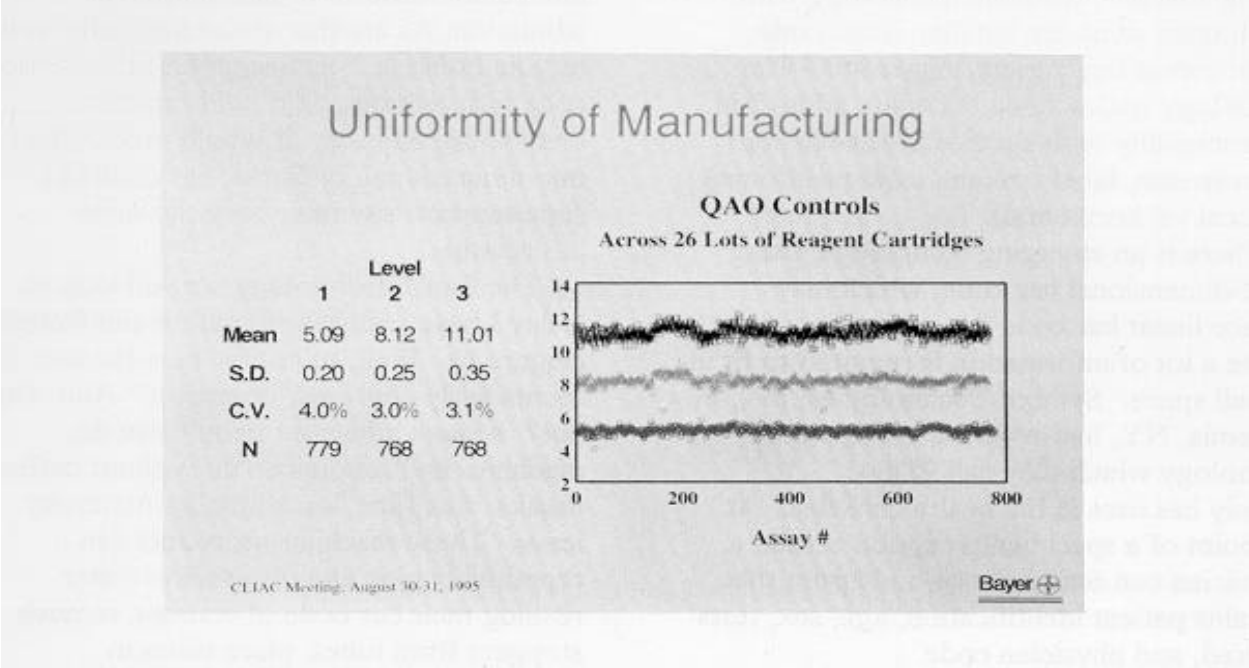


Figure 5. Results of quality assurance runs for product release over 2 years at 3 levels.

In a CLIAC presentation last month in September, Dr. Donald R. Parker, who heads the Clinical Trial units in our Northern Indiana site, made the point that the 2 levels of control each 24 hours is more than needed for systems which meet these technological advances. Using one of Bayer's systems as an example, we have found that many of Maclin's assumptions are met, and that the performance in the end-user's hands is simple. Figure 5 shows the results from the quality assurance control system run for product release at the plant over 2 years at 3 levels. In the clinical trial studies, similar tight control results were observed over nearly six months of work. The CV's were all about 3-1/2 to 4%. Compared with other methods in the field, the data from CAP proficiency surveys show for the Bayer system 4% CV for the low control and a 3% CV for the high control during the last few years. The take-home message here is that current CLIA regulations have not accommodated improving technology and still require 2 levels of control per 24 hours. Dr. Parker's presentation at the CLIAC meeting requested a change in the regulations to allow users to follow manufacturers instructions for QC.

The next technology type I will mention briefly is one I will call "Identification Technology". I don't see a need for bar code type technology in point-of-care settings, but for initial specimen identification needs in each other laboratory arena some type of machine-readable specimen identification will be required. Also, in the high-volume laboratories where serum separation and serum aliquotting are routinely necessary, further machine-readable specimen identification is required in the storage/retrieval and identification processes.

The machine readable technology with which most of us are familiar is bar code, which comes in a variety of systems. The technology issues being currently addressed are printability with successful readability down stream, label size and label positioning (vertical vs. horizontal).

There is an emerging technology, using the 2-dimensional bar code, which may replace linear bar code for applications where a lot of information is required to fit in a small space. Symbol Technologies, Inc., in Bohemia, NY, has invented a dense-code symbology which they call PDF417. It already has uses in the health care field. At the point of a specimen reception center, a technician can scan a dense-code print that contains patient identification, age, sex, tests ordered, and physician code.

The symbology is printed on the paper requisition in the scanner-readable rectangle, and also in the conventional human-readable type. In this scenario, much less time is spent in the accessioning and billing stations of the laboratory, and since repeat keystrokes are eliminated, the potential for keystroke error is averted.

Another application of this dense-code symbology is an extension of the Uniformed Military Identification Card system. That system is converting its credit-card sized identification cards to this technology, including an embedded digitized photo of the card owner. The Wilford Hall Air Force Medical Center at Lackland Air Force Base uses this to provide its patients with medical ID card containing their name, address, Social Security number, name of closest family member, and current medical status. This card saves time at registration in the outpatient clinic, but is even more dramatically useful in the emergency room (ER) when precious minutes are saved by immediate retrieval of information at admission. As another visual image for you to take home, a 2-inch square of this dense-code information could hold Lincoln's Gettysburg address. It would take 20 feet of one-dimensional, or linear, bar code like supermarkets use to encode the same information!

The fourth technology we will look at today I have called Automation and Robotics (Figure 6). Well, of course here the matrix seems fairly cluttered, doesn't it? And why not? Almost whatever people can do, machines and robots can do without coffee breaks, sick time, vacations, or maternity leave. These machines or robots can repetitively pick and place tubes (after reading their bar code of course), remove stoppers from tubes, place tubes in autobalancing centrifuges, aspirate serum or plasma and dispense aliquots into other tubes or cups, etc.

To give you a glance at what is now being done with automation, I've borrowed some slides on Total Laboratory Automation from Dr. Stan Bauer at Beth Israel Medical Center & Health Care Systems in New York. Beth Israel is installing an IDS sample handling automation system from Japan, distributed in this country by Coulter. This automation can duplicate almost any repetitive human physical activity needed to accomplish laboratory specimen handling processes. Automation can perform these specific laboratory specimen handling and tracking tasks when controlled by appropriate laboratory computers. The IDS system used in the Beth Israel Medical Center consists of a specimen transport chain moving the hockey puck tube carriers along from station to station. The tubes are kept upright and can be spun in this bar code reading station for the beginning of the

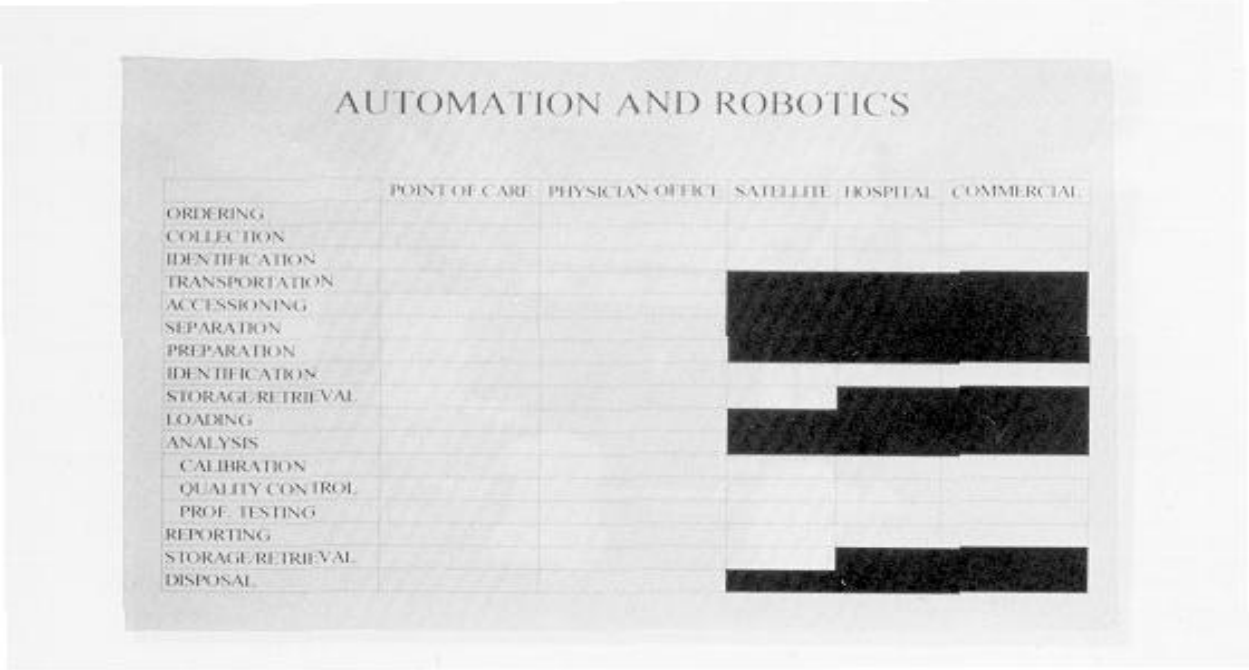


Figure 6. Automation and Robotics.

identification and tracking system, which directs the movement of each specimen.

The general laboratory layout is designed with separate lanes for the three major sections of the automated laboratory. One lane for urinalysis testing, the center lane for whole blood and plasma specimens used in hematology and coagulation testing, and the serum specimen lane for chemistry and toxicology testing. Each lane is served from the central input unit by a sorting lane system.

After entering the serum lane the tube stopper removal station and the serum level-detection station which provides information for down-stream stations to allow for rapid aspiration of serum by analyzers connected to the system.

A customized robotic interface which allows specimens to be placed in the correct position for aspiration into a chemistry analyzer is an integral component of this system.

Additional specimen handling systems are currently being developed. Another example of an approach to laboratory automation has been developed at the University of Nebraska Medical Center (UNMC) under the leadership of Dr. Rod Markin. UNMC clinical laboratory currently employs a front-end/accessioning area arrangement where specimens enter the system. The ceiling-mounted automated transport system moves the specimen carriers of the LAB-Interlink system (Figure 7). Here, an inverted robot station loads and unloads tubes from the specimen carriers. An articulated robotic arm can then load and unload samples from the specimen carrier into a test tube rack.

Many of you also know of the work being done at the University of Virginia (U.Va.) by Dr. Robin Felder and other U.Va. faculty on

Figure 7. Automated transport system.

the Remote Automated Laboratory System where no people are in these satellite labs except for routine maintenance and system checks. Dr. Felder has established a Research Center for Medical Automation Systems at U.Va. and I am grateful to him for providing the following slides of the Remote Automated Laboratory System. Health care professionals other than clinical laboratorians collect specimens, in this case from a patient in the emergency room, and take it to the analysis area. The touch screen allows the menu-driven software to guide the nurse through location selection, patient selection, and on to test selection, all in a very short time. After presentation of the sample to the aspiration tube of the analyzer, the nurse can return to other duties. Results are reviewed at the discretion of any member of the health care team. Speed of turnaround time, immediate availability, and simplicity of operation all result from taking a laboratory instrument and converting it to a nursing station system with user friendly software and remote monitoring of quality control to spot problems, should they arise.

By the way, Robin is hosting a symposium in October 1995 on laboratory automation which will include discussions of this Remote Automated Laboratory System and a demonstration of the IDS automation system at the U.Va. clinical laboratory. He told me that their IDS operations were made functional this past week , and claimed that they are the first laboratory in this hemisphere with a working IDS automation system.

Most of these technologies are being developed by various groups or companies with no existing standards to insure electronic interfacibility and mechanical compatibility. This area is being addressed

by a group of interested scientists and businessmen who formed as an offshoot from conferences on Laboratory Automation and Robotics.

They call themselves the Clinical Testing Automation Standards Steering Committee. Soon to be accommodated into the structure of the National Committee for Clinical Laboratory Standards, this automation standards steering committee is creating an organization of subcommittees to address the following issues:

Specimen Collection
Specimen Identification
Specimen Carrier
Communications
Mechanical Interface
System Status/Performance

The analogies to this effort are many, but the one I think most fitting for the mechanical issues is the beginnings of the railroad companies and their separate track development where different gauge tracks for each railroad company necessitated freight transfer between rail lines. Finally, a common gauge was agreed upon. Now, of course, a freight car can go on the same tracks as passenger trains and can go all over the continent, regardless of who owns the tracks or the trains.

This discussion on automation and robotics has so far focused on specimen handling and manipulation. Another area of robotics application involves transporting specimens from the point of collection to the laboratory. In a sense, this is a laboratory practice which takes place outside of the laboratory. Two of the most popular types of systems which come to mind are pneumatic tube systems and mobile robots.

Pneumatic tube systems have progressed a long way since the Lamson tube systemsdesigned for paper transport in banks and retail businesses. In a sense the evolution of reliability in these systems has come full circle. Early versions were simply point-to-point tubes, e.g., cash receipt-to-central accounting and return. Many hospitals adopted addressable systems which used central sensing and switching systems to route the “birds” from one station to another. The low reliability of these systems, which had the reputation for losing important lab orders or results, was their eventual downfall. Current systems combine the virtues of both earlier generation systems: single tubes to each station, and point-to-point simplicity. This combination is realized by computer-controlled, tube switches which allows the operator to send a bird to any other station by setting the address before sending the bird. The computer then sets its tube switches to the proper configuration, making a point-to-point system, and then sets the pneumatics in motion to pick up and deposit the tube, before another tube is accepted into the system. Another advance made in the modern pneumatic tube systems is controlled deceleration. Air cushions are used at the destination terminal to allow a soft landing of the bird at the station. This prevents the hemolysis likely to occur in a sudden stop that characterized early tube systems.

Mobile robots can also be used to move materials such as laboratory specimens and reports around a hospital building. They can be programmed to stop at specified stations and wait for someone to send them on their way after picking up or adding to the cargo, or they can proceed on a timed route with pre-programmed pause times at each station. Two types of mobile robots that are capable of moving through a building to pick up and

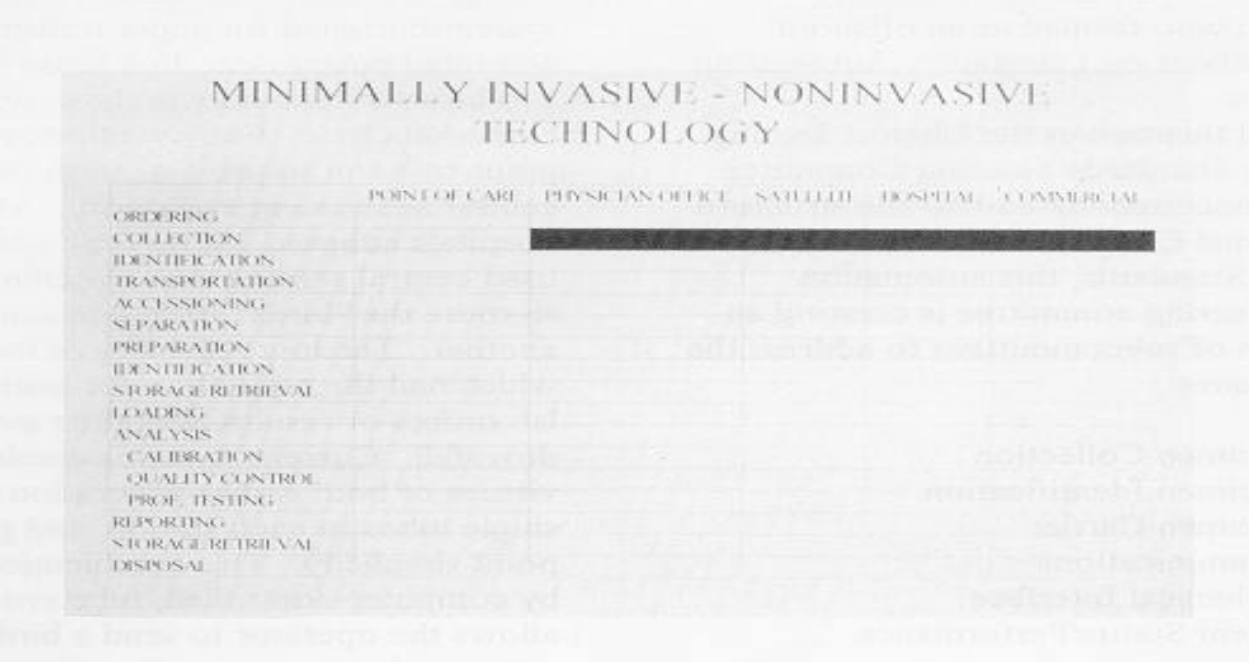


Figure 8. Effect of technology on specimen collection.

deliver specimens and reports.

The last technology I will present today covers the issue of the specimen itself. I'll call it minimally invasive technology, and it certainly will have an effect on the specimen collection issue outlined in this final matrix slide (Figure 8). Minimally invasive means to me capillary whole blood specimens collected by skin puncture. Early examples of the use of capillary tubes from skin puncture collection come from hematology and later blood gas testing. Microhematocrit testing on heparin-coated capillary tubes has been around for decades, and packed-cell volume is still the reference method for hematocrit testing. Similar capillary tubes have been used for blood gas analysis since the mid-1960's. Later in that decade the first reflectance meter for reading quantitative glucose results from dry chemistry reagent strips was introduced by Miles Laboratories for self-monitoring blood glucose. The technology for self-monitoring blood glucose has come a long way since those early years, but a simple skin puncture is still all that is required in the way of specimen collection.

A number of systems discussed earlier use capillary collection devices to get the whole blood to where it is needed for analysis. The I-Stat, Abaxis, and DCA 2000 are part of a trend of taking the laboratory to the patient instead of a tube of patient blood to the laboratory. A re-look at this matrix will tell you that many of the laboratory processes are simply by-passed or eliminated by this change in sample type, along with the change in physical location (bedside, home, etc.). The requirements here are that the technology be able to use whole blood and that the sample size be of microliter instead of milliliter scale, and collectable by skin puncture.

If we take this trend to its logical conclusion, we would not collect a specimen at all! In fact, non-invasive technology seems possible, even if difficult to commercialize and to obtain government clearance. Non-invasive technology would simply eliminate all of the processes from ordering to reporting except for the analysis itself. One example of the application of non-invasive technology that is close to commercial feasibility is near-IR reflectance measurements from the capillary bed of human tissue for determining whole blood glucose.

It may be possible to develop other ways to avoid specimen collection, and other analytes may be measurable by reflectance or other technologies.

In summary, I have presented five technologies which impact processes in laboratories ranging from point-of-care to commercial operations. These technologies are:

Communication
Microtechnology
Identification
Automation and Robotics
Minimally Invasive/Noninvasive

I will again invite you to consider these and other technologies which may improve clinical laboratory processes, such as these on the vertical axis of my matrix. As you participate in the various discussions over the next few days here at this Institute, perhaps ideas for applying technologies to specific cells in this matrix will emerge. If they do, please put those ideas on the table and let us see if any partnerships to take them forward can be forged between the laboratorians who need process improvements and those of you with theresources and the mission to participate in this type of enterprise. If the seeds planted today germinate, grow into something capable of process improvement and bear fruit, we will all benefit.

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2. Maclin E, Mahoney WC. Point-of-care testing technology. *J Clinical Ligand Assay*. 1995;18(1):21-33.