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SPECIAL ISSUE: PATHOLOGY

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COMMENTARIES

WINNING THE BATTLE BUT LOSING THE WAR: MANY SILVER LININGS ARE IN CLOUDS

A patient with Parkinson's disease has been suffering for years. Despite the best possible care, both in his doctors and at home, he declines, becomes increasingly dependent, and, perhaps worst of all, fluctuates so much and so randomly during the day that he may feel strong enough to go out shopping alone at one point but then "freeze" in place at the store and require rescue to bring him home by ambulance. This patient, mentally intact, is referred for deep brain stimulation surgery. He is tested in the standard fashion, which includes a very complete medical history, review of all PD drug regimens to see if other approaches may be tried, an evaluation with the patient off medication, an evaluation with the patient on medication, a neuropsychological examination, and a psychiatric examination, all before meeting with the neurosurgeon to review the procedure and the potential adverse consequences.

He goes through the procedure and is dramatically improved. His family reports that the day of the surgery is the date of his "rebirth." That day marks the beginning of his new life, a miraculous transformation from his pre-surgical bondage to his disease.

This is the stuff that doctors' dreams are made of (especially surgeons)! How god-like we are (sometimes)!

Unfortunately six months later things don't look so good. His Parkinson's is extremely well controlled. He doesn't fluctuate anymore. He is always "on." He drives, has resumed playing golf, and is well enough to go back to work. The patient is separated from his wife and children and is still not employed. He's depressed. His initial enthusiasm has vanished. As they say in the trade, "The surgery was a success but the patient died." It is a sad and fascinating phenomenon that was brought to my attention only recently. Some patients, with sudden and dramatic improvements

in health, may actually decompensate psychosocially. This happens in PD. It happens with epilepsy surgery as well. And I'll bet it happens with other dramatically transforming interventions too.

With the loss of disability and dependency a number of things may happen. When positive, the shackles are broken, the caregiver is freed, the patient returns to work or other gainful activities, the old family pattern is restored and everyone rejoices. In the negative world, the caregiver loses his/her role in life. No longer the suffering martyr, he/she now has to go back to work, spend more time with the extended family, and pay more attention to things less rewarding. The patient no longer has a slave-on-call. He no longer can say, "My PD is bad, please do this..." Suddenly there are responsibilities that haven't been there for years. Suddenly there is no longer a reason to justify special entitlements. Having to take an active and major role in family dynamics in place of a major but passive role may be unwelcome. Maybe the family no longer centers around the sick person anymore. The spotlight is off.

This has been described in epilepsy surgery as well. When patients are chosen carefully for epilepsy surgery, even those with daily, debilitating seizures may become seizure-free. In fact, about 75% do. Patients who may have had one or more spells daily, suffering from the terrible effects of the seizures plus the prolonged and sometimes equally disabling post-ictal states, become normal. Not only do the seizures and the post-ictal states stop, but the medication use goes down, along with their side effects of sleepiness, fatigue, mental dullness, incoordination, decreased interest, etc. With excellent seizure results coupled with a lack of neurological adverse effects, the benefits of epilepsy surgery are as dramatic as those in well-

chosen PD patients. Yet in one recent study, successful surgical outcomes were associated with a 2% suicide rate, 5% depression rate, 35% rate of "restructuring family dynamics" and a 12% grief reaction "over lost years."

When I think about these observations I conclude that while these outcomes are understandable, maybe even predictable to some of us, they certainly are a surprise to me. I do not reflect on these outcomes and say, "Gee, we should have thought of that. Of course family dynamics will change and those results are always unpredictable." I can't imagine myself or any of my colleagues sitting down to initiate our program in deep brain stimulation surgery in PD saying, "What are we going to do if these people get better?" After all, the whole point of the surgery is to make dramatic improvements. If we don't achieve this we shouldn't be offering it to our patients. We have learned, however, that we must discuss this issue with the patient, the caregiver and the family, but it's not clear to me what any of us can do with that information. Can anyone refuse a surgical candidate whose Parkinsonism we think will benefit from DBS surgery because we're afraid the support system will collapse, or the relationship with the spouse will implode, or something equally dire will occur? I think not, but we can recommend counseling and review the possible negative outcomes of a positive surgical result.

I haven't heard yet of anyone turning off their stimulator to become disabled, but I won't be surprised when it happens.

JOSEPH H. FRIEDMAN, MD

THE DANCING CATS OF MINAMATA BAY

Minamata had been a peaceful little Japanese village supporting itself by fishing within its neighboring bay, by harvesting salt in one of its shallow coves and by some subsistence rice farming. Salt production, their only source of negotiable funds, was shortly to become a government monopoly and so the leaders of this coastal community sought alternate sources of income.

Following the Russo-Japanese War [1904 – 05], Japan underwent a rapid expansion of its industrial base. Minamata, on the southwest coast of Kyushu, eagerly agreed to donate land as the price for attracting a new industrial plant manufacturing carbide. The demand for carbide, however, diminished during the next decade and so the factory switched its production line to ammonium sulphate, an agricultural fertilizer. During World War I, the importation of fertilizers to Japan was halted and thus the company [now called Nippon Chisso] achieved great prosperity since it held a near monopoly on the manufacture of fertilizers.

Following World War I, Nippon Chisso [*Chisso* is the Japanese word for nitrogen] aggressively expanded its operations into Japan's Asiatic colonies, particularly Korea, where it established massive factories powered by cheap hydro-electric power. In 1927, through the use of a high-pressure gas process, Nippon Chisso grew to become one of Asia's most powerful chemical manufacturing corporations.

A crucial change took place at the Minamata plant complex in 1930. It was discovered that a variety of organic chemical compounds could be elaborated by passing acetylene [derived from the calcium carbide] over mercuric sulphate. Among these newly synthesized products was vinyl acetylene, an essential ingredient for the manufacture of plastics.

As the Chisso production facility in Minamata expanded, so did the village. From a small, anonymous community, Minamata grew to become a town and then, during the second World War, into a prosperous city. But from the beginning it was a city wholly dependent upon a single industry. Indeed, the civic leadership of Minamata was always controlled by Chisso and criticism of Chisso or the working conditions within its plants was regarded as tantamount to heresy.

Japan in the 1930s was transformed into an industrial-military nation. By 1938, in association with the German chemical corporation, I.G. Farben, the Minamata complex augmented its output of vinyl chloride and other components essential for military use.

The local fishermen were the first to declare that something was amiss. They noted dead fish floating on the surface of Minamata's bay. And, to their increasing dismay, their fishing yield progressively diminished. The local association of fishermen sent a delegation to Nippon Chisso claiming that the loss of fish was caused by industrial wastes emptied into the bay. The company vehemently denied the charges and declared the fishermen to be unpatriotic. Nonetheless, in 1927 and again in 1943 Chisso quietly provided a meager stipend to the fishermen, with the stipulation that there be no further requests for compensation.

The Nippon Chisso factories in Minamata were destroyed by American air strikes in 1944, leaving the community without a source of income. But during the extended occupation of Japan by Allied Forces, and prompted by extensive unemployment, the Minamata complex was allowed to be rebuilt in 1949 for the production of polyvinyl chloride. By 1953 Minamata became the major Asiatic source for the production of PVCs. The Nippon Chisso factories now provided 60% of Minamata's tax-base; and the city's mayor and most of its Municipal Council were either current or past employees of the company.

By the mid-1950s yet another disturbing event surfaced. Citizens noticed that many of the town's cats behaved strangely. For no apparent reason they exhibited frenzied behavior, throwing themselves against stone walls, prancing or staggering as though intoxicated, and frequently hurling themselves into Minamata Bay, where many drowned. What may have been faintly amusing at first rapidly produced much concern by the more thoughtful people of Minamata.

In May 1956, the Minamata City Hospital [managed and funded by Nippon Chisso] admitted four patients with essentially similar presenting signs and symptoms. These four had been healthy until they experienced the sudden onset of stumbling gait, confusion, fever of unknown origin, convulsions, stupor which deepened into irreversible coma and death. Within weeks there were a total of 17 deaths. A hasty epidemiologic inquiry found two things which all of these dead patients shared: They were all longtime citizens of Minamata and their principal diet had been fish derived from the Bay.

The yield of fish in the Bay diminished so drastically that on November 2, 1959, 4,000 desperate fishermen stormed the Chisso factory demanding compensation for the loss of their income. The public denounced the action of the fishermen, the leaders of whom were duly punished, but a feeling of disquiet became pervasive in Minamata as the number of unexplained deaths increased. The chief physician of the city hospital, Dr. Hosokawa, fed some of the factory waste products to a few cats, saw them develop a frenzied behavior, and at autopsy, exhibited the characteristic signs of mercury poisoning. He was, however, forbidden to publish his findings.

Years later, a careful toxicological survey disclosed that the fish and shellfish of the Minamata Bay were heavily contaminated with methyl mercury, as were the internal organs of the frenzied cats and the local fish-eating citizens. Thus far, 1,760 victims have been identified but a local university places the victims at over 10,000.

Nippon Chisso ceased manufacturing products requiring mercury in 1969, concentrating now on the synthesis of fertilizers and other industrial chemicals. The sediment of the Bay is still heavily contaminated with methyl mercury, earth fill has covered the shallow inlets of the Bay, a memorial park has been established and local fishing has long since been prohibited. The victims have been financially compensated but the unhappy incident is rarely discussed locally.

STANLEY M. ARONSON, MD

INTRODUCTION

RONALD A. DELELLIS, MD, CYNTHIA L. JACKSON, PHD, AND
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The past several decades have witnessed the development of an impressive array of advances in the laboratory sciences which have dramatically changed the practice of pathology. During this time, departments of pathology and laboratory medicine have evolved into highly complex organizations which provide anatomic and clinical pathology laboratory services to virtually every hospital department, outpatient clinics and a variety of outreach facilities. The clinical laboratory disciplines include Transfusion Medicine, Clinical Chemistry, Hematology, Coagulation Medicine, Clinical Immunology, Clinical Microbiology, and Molecular Diagnostics. Anatomic Pathology areas include Surgical Pathology, Cytopathology and Autopsy Pathology. In their daily functions, each of these laboratories serves as a bridge between developments in the basic and applied biological sciences and the practice of clinical medicine.

The techniques of flow cytometry, molecular biology and proteomics, together with the availability of highly sophisticated robotic and laboratory information systems, are transforming the laboratory landscape. Molecular biological methodologies, in particular, have become rapidly integrated into the contemporary practice of pathology and laboratory medicine. This process has accelerated in recent years with the development of high throughput molecular approaches and global initiatives, including the Human Genome Project. Techniques are available to target specific segments of DNA and to amplify and analyze them with respect to the presence of mutations, translocations and other abnormalities. Microarray technologies permit pathologists to unravel the complex gene expression profiles seen in most malignancies. These studies have been of particular value in separating tumors into prognostically distinct types despite the presence of similar or even identical morphological features.

In anatomic pathology, molecular data are now being incorporated into diagnostic reports to refine and enhance

both morphological and prognostic assessments. Information on Her2/neu copy number, for example, has become an integral component of standard breast cancer reports. In clinical microbiology, molecular techniques are used for the rapid identification of infectious agents, measurements of viral loads, characterization of resistance mutations in viruses (HIV) and bacteria (methicillin resistant staphylococcus aureus), and the characterization of HPV subtypes in cervicovaginal smears. Molecular approaches will also play key roles in bioterrorism preparedness programs in which accurate and rapid identification of infectious agents will be an absolute necessity.

In hematology, molecular approaches are used for the detection of specific gene rearrangements. These methods have been of value not only for diagnosis but have also formed the basis for the detection of minimal residual disease. For example, sequential monitoring of the levels of BCR/ABL messenger RNA in patients with acute myeloid leukemia correlates with the re-emergence of malignant clones and can predict impending relapse. Additionally, these methods are essential for identification of a variety of heritable disorders such as cystic fibrosis. The challenges for pathologists and clinicians alike will be to relate novel molecular data to disease states and to develop technologies and strategies that will take full advantage of this information in a cost-effective manner.

The laboratory profession has had a long and distinguished history of high quality practice with an emphasis on internal quality control and the organization of proficiency testing programs. An important recent development has been the use of automation combined with highly sophisticated laboratory information systems. As discussed in a subsequent paper in this issue, automation of many aspects of laboratory testing has provided a crucial approach to the elimination of potential failure points in processes where errors could be made. While much remains to be accomplished, the clinical laboratory has done more than

many other sections of the health care industry to decrease the occurrence of errors.

It is indeed sobering to consider the fact that approximately 70% of all medical decisions are based directly or indirectly on results obtained from the clinical laboratories. This presents both a unique challenge and an awesome responsibility for the entire laboratory staff which must provide accurate, reproducible and cost effective results with rapid turnaround times on a 24/7 schedule. It is also clear that the role of the clinical laboratory is expanding in all areas of patient care as the number and diversity of diagnostic tests increases.

To provide a balanced view, however, it must be pointed out that the disciplines of pathology and laboratory medicine face a series of critical challenges, which have resulted, in part, from a series of market forces: decreasing government reimbursement rates for clinical laboratory services, staffing shortages, growing investment in **point-of-care testing (POCT)** procedures and ever increasing regulatory standards.

Declining government reimbursement rates are of great concern to clinical laboratories, as they are to all areas of the healthcare industry. Congressional initiatives to institute copays for Medicare-reimbursed laboratory tests and to freeze the Medicare Clinical Laboratory Fee Schedule create further competition with the potential for lowering quality of services. In order for laboratories to survive, they will need to perform more tests, have fewer testing sites, operate with fewer instruments, have lower operating costs and use more automation. Implementing these strategies requires considerable capital, and many laboratories have difficulty in securing this funding. Without the funding to improve productivity and lower operating costs, the laboratory's ability to provide high quality service while generating a profit will be jeopardized.

By the year 2010, an estimated 50% of current clinical laboratory scientists and technicians will be eligible for retirement. This exodus, combined with a shrinking pool of candidates

considering entry into the laboratory professions, will have devastating effects. Fewer students are entering the field because of issues related to pay and schedules, the stressful working conditions, few opportunities for advancement in the hospital setting and the potential health risks. Recruitment and retention strategies must be improved in order to provide the very best laboratory services. Emphasis should be placed on raising public awareness of the laboratory profession and providing more comprehensive information about the profession into the hands of individuals who influence career decisions, including high school guidance counselors and college advisors.

Hospitals continue to invest in POCT due to pressures from clinicians for immediate results and the premise that faster testing and result reporting translate into improved patient outcomes. This creates a challenge for the clinical laboratory because it is ultimately responsible for maintaining compliance with regulatory standards (i.e. quality control, training, documentation,

etc.), ensuring the overall quality of test results from the testing devices, and having the ability to capture the results in the medical record. In most cases, the hospital laboratories that hold the necessary licenses to perform the testing lack the ultimate control of their utilization. Reducing pre-analytical (i.e. transport and specimen processing) times and providing laboratory results directly to the physician via electronic communication can substantially reduce the further expansion and considerable expense of POCT procedures.

Despite these many challenges, we also recognize many opportunities. The advances in pathology and laboratory medicine have been nothing short of spectacular, and we remain optimistic that laboratory based physicians and scientists will continue to be leaders in healthcare and patient safety initiatives. This can be accomplished by introducing state of the art testing strategies and continued laboratory automation, promoting quality improvement initiatives and fostering the development of effective and safe laboratory utilization programs.

In his great painting in Boston's Museum of Fine Arts, Paul Gauguin posits three questions "Where do we come from? What are we? Where are we going?" In this issue of *Medicine & Health/Rhode Island*, we hope to address some of these questions with respect to the practice of pathology and laboratory medicine.

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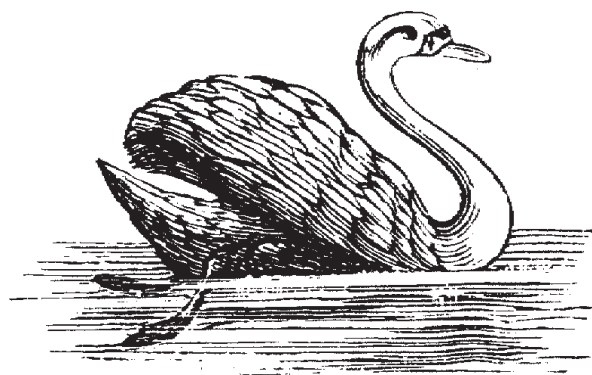
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GENE MICROARRAYS IN TUMOR DIAGNOSIS: OPPORTUNITIES AND CHALLENGES

DILIP GIRI, MD

EVOLUTION OF SURGICAL PATHOLOGY

Morphologic pathology has advanced considerably since the latter part of the 19th century when in the midst of significant initial skepticism in some quarters, surgical biopsy was introduced as a diagnostic tool in continental Europe. In the US, the formal institution of surgical pathology as a diagnostic discipline in clinical practice, can be traced to the appointment of Joseph Bloodgood as the first full-fledged surgical pathologist at Johns Hopkins Hospital in Baltimore, Maryland, by William Halsted the pioneer in breast cancer surgery.¹ It is interesting, although not common knowledge, that the advent of surgical pathology was facilitated by the development of the freezing microtome in the early years and that frozen sections were an important and in some instances the sole means of obtaining tissue diagnoses. According to anecdotes, the ability of a pathologist to render a definitive intra-operative diagnosis in a matter of minutes (rather than days taken by the 'academic' pathologists) greatly enhanced the relevance and value of surgical pathology.² Over the last several decades advances in histological techniques have helped to establish morphologic pathology as the single most important tool in the hands of the surgical pathologist. In fact, the terms morphologic pathology and histopathology are used synonymously with surgical pathology.

The pathologic evaluation of cancer is based on assessment of a series of morphologic parameters of an individual tumor, including the tumor size, type, grade, involvement of lymphovascular channels and the status of regional lymph nodes. These assessments are made using the standard **hematoxylin and eosin (H&E)** stain on tissue sections. While this is the usual approach, in some instances additional studies are performed as

diagnostic and prognostic parameters, including electron microscopy, *in situ* hybridization, **polymerase chain reaction (PCR)**, cytogenetics and proteomic analyses. In breast cancer, for example, the expression of **estrogen and progesterone receptor proteins (ER/PR)** as well as that of Her-2/neu gene product are tested using immunohistochemical methods. Although conventional H&E stain-based morphologic pathology is the single most important approach in surgical pathology, it has evolved and increased its strength by being able to "absorb" and incorporate numerous newer technical advances. In many ways these "advances" are imprints left by the technologies that were developing or had been developed at the time.

**"... GENE PROFILING
WILL BECOME A
KEY APPROACH IN
UNDERSTANDING
THE BASIC BIOLOGY
OF TUMORS"**

In the early decades of the 20th century, various histochemical tests that permitted the detection of microbial organisms or intra-cellular constituents such as mucin, glycogen or fat were added to surgical pathology. At the time, these newer tests were used with great enthusiasm, for example, in distinguishing an adenocarcinoma from non-adenocarcinomas or in discriminating Ewing's tumor from other similar appearing soft tissue/bone tumors. With advances in immunology in the second half of the last century, antigen-antibody reactions were adapted to tissue sections on the premise that the localization of a single antigen or groups of antigens would enable distinction of various cell

types. This, in turn, would provide the pathologist with an objective diagnosis of the tumor type in contrast to the morphologic diagnosis which is based on subjective assessment of patterns. Similarly, when electron microscopes became available, they were quickly employed in diagnosing lesions based on their sub-cellular features. The same paradigm applies to the use of molecular techniques such as *in situ* hybridization and PCR.

During the evolution of surgical pathology its relevance as a diagnostic modality has been questioned on many occasions. The fact is, however, that surgical pathology has flourished over time and has either absorbed some of these techniques with the goal of increasing its own vitality or seen the demise of some of the very applications that threatened its relevance in clinical oncology. An example is the biochemical assays for ER and PR in breast cancers used in the 1960s and 1970s. These assays were performed by biochemists because morphologic predictors of ER/PR status were considered unreliable. However, with the immunohistochemical assays for these markers in the early 1980s and their rapid application to paraffin sections, the biochemical assays were rendered obsolete.

Over the years, our understanding of tumor biology has increased exponentially. We now know that various pathways involving many molecules play vital roles in the growth and development of tumors. In recent years, oncologists have targeted some of the key molecules involved in tumorigenesis in devising novel forms of therapy.⁴ An example in breast cancer is Her2/neu, a key tumor growth factor receptor. An anti-Her2/neu monoclonal antibody (commercially available as Trastuzumab or Herceptin) is used in the treatment of a subset of breast cancer patients with evidence of dramatic responses. Since purely morphological

methods do not allow elucidation of the pathways or processes involved in tumorigenesis, these adjunctive approaches are used in tandem with conventional morphology to give us only snap-shots of molecules important in tumor growth. Following the sequencing of the human genome, the development of DNA microarrays on silicone chips have permitted gene profiling of cancers. It is likely that gene profiles will permit the identification of hundreds of genes involved in tumorigenesis and will also elucidate their interrelationships. It is likely that gene profiles will permit molecular classifications of tumors and that these approaches may supplant the current morphologic ones. Studies have also shown that gene profiling may help to identify genes that are responsible for organ specific metastatic potential of tumor cells.³ It is clear, therefore, that gene profiling will become a key approach in understanding the basic biology of tumors, in the clinical diagnosis of tumors, and in the development of novel therapeutic strategies. However, the results from c DNA microarray studies must be thoroughly validated since there is potential for the incorrect selection of candidate components within the tumor. The role of the surgical pathologist in this validation process will be crucial.

GENE EXPRESSION ANALYSIS: MORPHOLOGY VERSUS GENE (DNA) MICROARRAYS

By conventional light microscopy, the diagnosis of tumors is based on the recognition of specific patterns that are universally acknowledged as being characteristic of the particular entity. Considering the fact that a bewildering array of morphologic phenotypes are seen in tumors arising in a given organ, it is tempting to argue that the various patterns are, in fact, the ultimate expression of the underlying genotype. Figure 1 shows some of the less commonly encountered histologic types of breast carcinoma (A: Invasive lobular carcinoma, B: Invasive micropapillary carcinoma, C: Medullary carcinoma and D: Mucinous carcinoma). The recognition of these

morphologic types has prognostic significance based on the retrospective analysis of thousands of such cases across numerous studies independently carried out by pathologists over a period of many years. Some of these tumors, such as the invasive micropapillary carcinoma, are known for their aggressive behavior, while others such as mucinous carcinoma and medullary carcinoma are associated with a favorable prognosis. Invasive lobular carcinoma, although not prognostically distinct, appears to be biologically distinct in that these tumors have a predilection to metastasize to unusual sites such as the stomach, endometrium or cervix. It would be interesting to determine if the gene profiles for each of the morphologic types is different and, if so, what the differences are.

Morphology also reveals the topographic relationship and the nature of the tumor stroma. For example, in Figure 1A the stroma is fibrous and is significantly greater than that in Figure 1B. On the other hand the stroma in figure 1C is composed of lymphocytic infiltrates whereas that in Figure 1D is composed of acellular mucin. The recognition and in depth knowledge of these morphologic attributes of tumor will be of great importance in analyzing the data that gene profiling studies deliver.

GENE MICROARRAYS: HOW THEY ARE PERFORMED

In contrast to morphology, DNA microarray studies directly demonstrate the over- or under-expression of thousands of genes or gene related sequences in comparison with another tumor or the baseline for that particular organ. Gene microarrays are performed using various types of expression arrays, the most common of which is the oligonucleotide array. Briefly, fresh or frozen tissue samples enriched for a representative area of the tumor are homogenized and subjected to a standardized protocol for extraction of **messenger RNA (mRNA)**. The mRNA in the samples is then reverse transcribed to **complementary DNA (cDNA)** and biotinylated. The biotinylated sample is then incubated with a silicon or nylon

membrane chip typically arrayed with millions of copies of oligonucleotide probe sets. The number of probes on a given platform (silicon chip) varies but usually several thousand probe sequences are arrayed on an individual platform. After the completion of incubation, a chromogenic or fluorescent reaction using conjugated streptavidin is carried out and the subsequent reaction is image analyzed. (Figure 2).

STATISTICAL ANALYSIS AND GENERATION OF DENDOGRAMS

A computer program uses algorithms to cluster differences in expression patterns between sample sets based on the level and similarities of expression patterns between samples. This approach is called the unsupervised clustering or classification. In the supervised methods of analysis, gene expression differences are studied in pre-determined groups (typically based on available clinical information such as bad prognosis and good prognosis tumors). Once the clusters are determined, they are supplemented by visual display using tree-like dendograms. (Figure 3) The statistical methods are still evolving and no single statistical method is applicable to all situations. One of the major weakness of the statistical tests used in gene expression analysis is that whereas there are thousands of gene sequences, the total number of samples is relatively small.

GENE MICROARRAY: CURRENT STATUS

The number of studies on the subject of gene microarrays has increased exponentially in the last 3-4 years: over 400 studies focus on breast cancer alone. Several studies have demonstrated the considerable power of gene microarray analyses. For instance, in a study of morphologically similar appearing non Hodgkin's lymphomas of the diffuse large B cell type, two subtypes defined by differing patterns of gene expression were identified.⁵ One subset had gene patterns similar to those of germinal center cells (called as the germinal center diffuse large B-cell lymphoma) and the other had gene profiles similar to those seen

in the peripherally activated B-cells (called the activated diffuse large B cell lymphoma). The activated cell type had a significantly worse prognosis based on the results of this study. Analyses of this type highlight the clinical significance of gene profiling studies and their superiority over conventional morphologic studies in predicting prognosis.

In another study, gene expression profiles of more than 175 cancers from 10 common sites including 12 metastatic tumors were studied.⁶ The authors were able to accurately identify the organ of origin in over 90% of cases, an astoundingly high accuracy rate. Using morphology and state of the art immunohistochemistry accurately predicting the site of origin of a metastatic lesion is often frustratingly difficult, especially in poorly differentiated tumors. In another study, a total of 295 early breast cancer cases (stage I/II) were analyzed.⁷ Based on the profiles using a set of signature genes, it was possible to divide the patients into poor and good prognostic groups. Eighty-five percent of the good prognosis patients survived disease free for over 5 years while only 50% of the patients in the bad prognosis group had more than 5 year survival. A study done by Sorlie et al⁸ proposed a molecular classification for breast cancer dividing the cases into two broad categories one with the 'luminal' type cytokeatin expression (generally ER positive) and the other with a 'basal'

type cytokeatin expression (generally ER negative). It is clear that gene expression studies represent a major advance in the study of tumors. It appears that using this approach, it will be possible to predict prognosis, to classify tumors into biologically relevant groups, and, as described in another recent study, to identify genes that are responsible for organ specific metastatic potential.

VALIDATION OF GENE MICROARRAY DATA

It is critical to validate data on gene expression. A reference sample must always be assayed with the test sample as an essential quality assurance control. Ideally, all samples should be run in duplicate on different chips and the expression patterns should be compared to ensure that there are no "between run" differences. It is important to validate gene expression by actually demonstrating a gene product in tissue sections either by using in situ hybridization for the corresponding messenger RNA or by performing immunohistochemistry for the corresponding protein. An elegant approach is to prepare multitissue blocks, also referred to as tissue microarrays (Figure 4). Briefly 3mm cores of comparable areas of tumors that were subjected to gene expression analysis are obtained from paraffin embedded blocks and are re-embedded in a separate block. Potentially, several hundred tumor samples can be

embedded in one block, and sections obtained from such blocks can be examined immunohistochemically or by in situ hybridization to verify differences in gene expression patterns (Figure 5).

PROBLEMS AND PITFALLS IN GENE MICROARRAY STUDIES

The published studies on gene micro arrays indicate that our understanding of tumor biology will be enhanced greatly using this technology. Morphologic methods may be supplemented or even supplanted by gene profiling studies; however, there is a need to understand several issues. First, only a few hundred cases have been examined for any given type of cancer and it would be incorrect to make generalizations based on these relatively few examples. Under the present circumstances it will probably not be feasible to study a large number of cases because of the need for fresh or frozen tissue samples. Tissue repositories with large numbers of tumors are relatively few; moreover, the study of banked specimens may not allow sufficiently long term follow-up studies.

Most tumors are morphologically heterogenous. Unless the sampling is performed by a trained surgical pathologist the results may be misleading or spurious. Even with good sampling, tissue contamination by stroma or other elements may be unavoidable. In such instances, it may be necessary to use laser capture microdissection to isolate pure tumor populations. Laser capture equipment is expensive and not available in most pathology laboratories. Finally, today's statistical methods are not uniform, and there is ongoing discussion on what may be the best approach to analyze the data obtained from these studies.

In conclusion, the routine use of gene profiling as a clinical tool may not quite be around the corner. Meticulous planning and well-supervised execution of these studies with a major input from a surgical pathologist is essential for the new technology to render the goods.



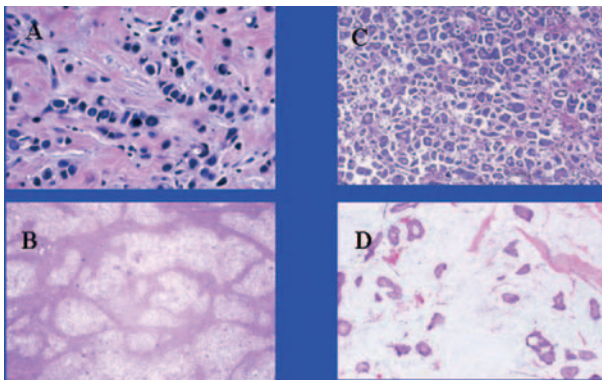


Figure 1. Morphologic sub-types of breast carcinoma (Ca).
 A. Invasive lobular ca B. Medullary ca
 C. Invasive micropapillary ca D. Mucinous ca

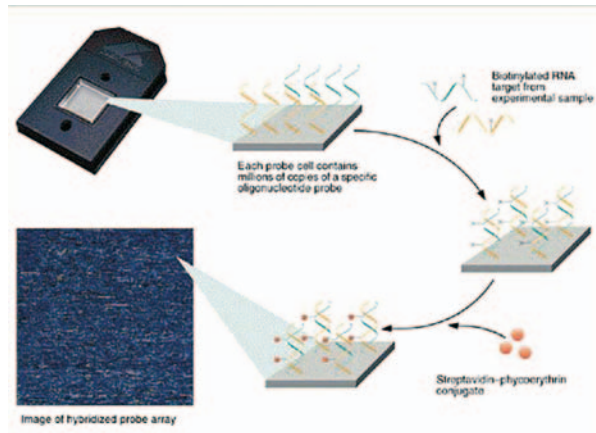


Figure 2. Protocol for performing gene micro arrays (see text).

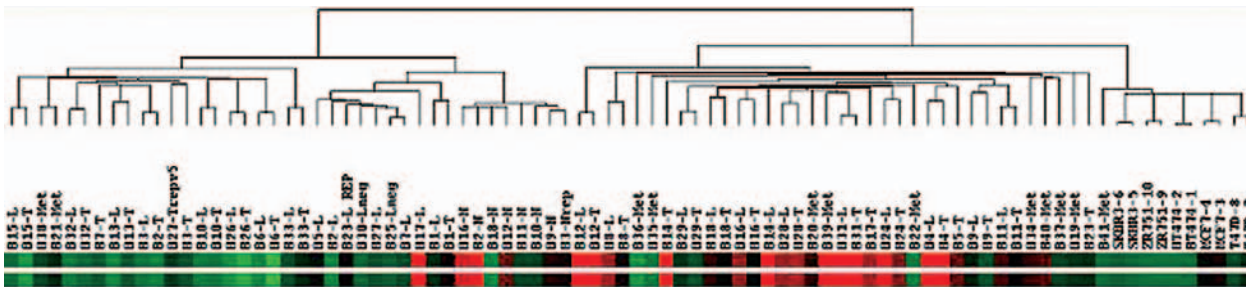


Figure 3. Tree like dendrograms showing the clustering of individual samples with the others depending on the closeness of the gene profiles.

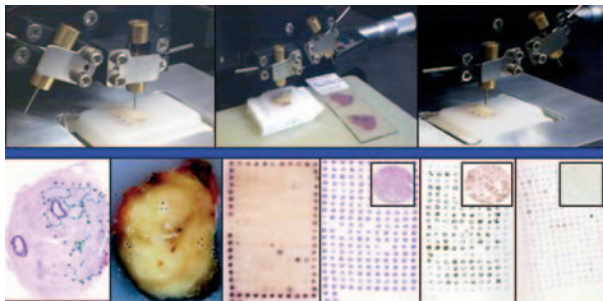


Figure 4. Construction of a tissue block for tissue micro array (TMA) studies.
Note: The width of each block is 25mm.
Each core of tissue measures 0.6mm

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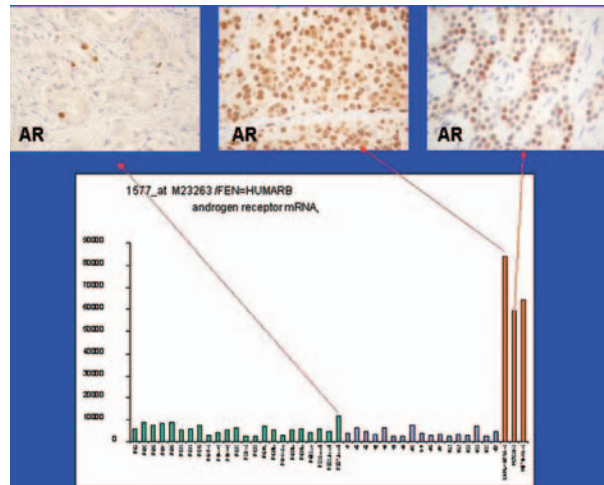


Figure 5. Correlation between protein expression on TMA using antibody to AR (top panels) and the gene expression of corresponding samples by gene micro array studies. TMA was used to validate results of AR expression using antibody to AR (top panels) and the gene expression

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CONTRIBUTIONS OF PATHOLOGY AND LABORATORY MEDICINE TO THE PATIENT SAFETY MOVEMENT

NOUBAR KESSIMIAN, MD, AND RONALD A. DELELLIS, MD

The 1999 **Institute of Medicine (IOM)** report, "To Err is Human: Building a Safer Health System" projected that up to 98,000 unnecessary deaths occur in US hospitals as a result of medical errors.¹ Error was defined as the failure to complete a planned action as intended or the use of the wrong plan to achieve an aim.¹ Although medication errors are among the most common types, significant errors occur in all areas of medicine, including pathology and laboratory medicine. Pathology laboratories offer more than 3,000 tests to medical practitioners and patients with an estimated volume of 8 billion tests per year in the United States alone. This number includes surgical pathology and cytopathology, chemistry and toxicology, hematology and coagulation, microbiology, histocompatibility analyses, immunology, flow cytometry, molecular pathology, reproductive medicine and transfusion medicine. Clearly, the pathology laboratory plays a crucial role in overall patient safety and outcome, because the clinical laboratory provides an estimated 70% of all information used in decision-making for admission, treatment and discharge of patients.²

CLINICAL LABORATORY MEDICINE

The laboratory profession has had a long, distinguished history of high quality practice with an emphasis both on internal quality control and on the organization of proficiency testing programs.³ In 1947 Belk and Sunderman first published the results of a clinical chemistry survey in the US.⁴ The **College of American Pathologists (CAP)** promotes quality laboratory service through an accreditation process with emphasis on peer review and education. All US clinical laboratories must be certified by the **Centers for Medicare and Medicaid Services (CMS)** under the Clinical Laboratory Improvement Amendment of 1988

(CLIA-88). Congress passed CLIA in 1988, establishing quality standards for all laboratory testing in order to ensure the accuracy, reliability and timeliness of patient testing, regardless of where the tests are performed. CAP as well as other accrediting entities maintain deemed status from CMS. In general, the CAP guidelines and requirements are more rigorous than the CLIA-88 regulations. In addition, some states, Rhode Island included, have specific licensing requirements for laboratory personnel.

**"ALTHOUGH
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Most of the voluntary, educational and regulatory activities, as well as advances in instrument technology and automation of the testing process, have been directed almost exclusively to the analytical phase of the testing cycle and have contributed to the low level of errors seen in this phase. The analytical phase includes all laboratory specific steps. The pre-analytical phase, on the other hand, includes all the steps that occur prior to the actual analysis of the sample in the laboratory. This phase includes a host of patient-related and processing-related variables, including patient identification, specimen collection and sample labeling. The post-analytical phase begins when the test result is obtained and ends when the physician receives it.

The distribution and frequency of errors in the clinical laboratory

has not been studied extensively or rigorously; however, almost all authors agree that most errors (65%) occur in the pre-analytical phase of the testing cycle while the lowest level of errors (6.7%) is seen in the analytical phase.⁵⁻⁶ Approximately 27% of the pre-analytical errors are due to patient misidentification and specimen mislabeling.⁷⁻⁸ The reason for the low proportion of analytic errors is the fact that directors of clinical laboratories and manufacturers of testing reagents and equipment have focused on this phase of the testing cycle. Additionally, laboratory directors have almost complete control over this phase of the cycle. The high frequency of errors in the pre-analytic phase are the direct result of the complexity of the testing environment. Specimens are collected routinely by individuals who may not be trained as phlebotomists or laboratory technologists. Moreover, the handling and transport of specimens to laboratories are not without problems: inappropriate collection techniques, traumatic blood draws and transportation delays may each contribute to erroneous values. In contrast to the analytic phase, most of the pre-analytic variables are not under the direct control of the laboratory director. These observations underscore the need for intensive patient safety initiatives particularly in this phase of the cycle.

Data on error rates in the clinical laboratory reportedly range from 1/164 to 1/8300. The risk of errors is dependent on the methods used for their detection and the definition of what constitutes an error; there is considerable variation in both of those parameters in different laboratories. Many laboratories have adopted the Six Sigma quality management program to evaluate and reduce lab errors. In the 1980s the Motorola Company implemented the Six Sigma program to develop the best processes that would allow the manufacturer to produce

almost no defective products.⁹ This program seeks to build quality into processes with the goal of eliminating defects by reducing variation. While the Six Sigma allows the measurement of defects,¹⁰ the Lean system identifies opportunities to streamline the workflow and to improve both efficiency and quality.⁷ Performing instantaneous root cause analyses and developing error reduction strategies are the key to these approaches. Manufacturing companies have embraced both Six Sigma and Lean methodologies to improve their products, to be competitive and improve their bottom line. A number of medical laboratories are implementing the Lean methodology in addition to Six Sigma.⁷

The average American manufacturing company operates at the Four Sigma level or at 6,210 DPM (Defects per Million)⁸ while the commercial airline industry operates at better than Four Sigma level (3.4 DPM). The risk of dying in a commercial plane crash is 0.14DPM. The aviation industry vigorously investigates its bad outcomes and also its near misses. Although clinical laboratories investigate their bad outcomes, their near misses have been generally ignored. The majority of laboratory procedures operate at less than the Four Sigma level (6210DPM); clearly, there is ample opportunity for improvement. Achieving a Six Sigma level should be the goal for pathology and laboratory medicine. This can be accomplished under the leadership of the pathologist if a management style that promotes and actively supports an effective error reduction and continued improvement program is adopted. This approach also requires support of the hospital administrators. Errors and near misses should be documented, reported and investigated at each step of the process. Corrective actions should be taken and the effectiveness of the corrections monitored. It is critical to change the culture of blame, punishment and litigation, all of which have failed to improve patient safety because most failures are ingrained system problems.

SURGICAL PATHOLOGY AND

CYTOPATHOLOGY

Very few studies focus on the issue of errors in anatomic pathology, and results from different published series are difficult to interpret and compare.¹¹ Similar to clinical laboratory medicine, errors in anatomic pathology can occur at any point in the testing cycle between obtaining the specimen and receipt of the final report.^{12,13} Pre-analytic errors can occur prior to specimen receipt in the laboratory as a result of patient misidentification and specimen mislabeling in the operating room, radiology suite or clinic. The net result of this type of error is that the specimen in the container does not belong to the patient whose name appears on the container or accompanying requisition form. Pre-labeling of specimen containers is a significant source of this type of error. Such errors are virtually impossible to detect by the pathologist and may ultimately come to light only when the clinician reports that a particular patient did not have a biopsy corresponding to the submitted report. Pre-analytic errors can also occur as a result of incorrect site/side designations or inadequate or even incorrect clinical information on the accompanying labels or requisition forms.

Errors can occur at multiple points in the pathology laboratory, including specimen accessioning, gross dictations, block embedding and labeling and slide preparation and labeling. In contrast to the clinical laboratory, which has embraced automated methods, virtually all of the work flow in anatomic pathology laboratories is manual. It has been estimated that a biopsy specimen must pass through almost twenty separate steps before the slides are available for review. The application of Lean production methods with immediate root cause analysis and the institution of error reduction strategies has the real potential of reducing these types of errors.¹²⁻¹⁴

Although specimen identification errors most likely occur at very low frequencies, the potential of harm to the patient is very real; e.g., a mastectomy or prostatectomy on the wrong patient. The true scope of this type of problem,

however, is not known with certainty due to the lack of rigorous studies of these types of errors.¹⁵

Post-analytic errors may occur during dictation and transcription and also include provision and receipt of reports. Problems with the receipt of reports may occur as a result of the incorrect physician receiving the report because of incorrect physician contact information. In many pathology departments, both "hard" copies and faxes of reports are sent to the physician(s) listed on the initial requisition. In some departments, unexpected (critical) findings and new diagnoses of malignancy are also called directly to the responsible clinician. This is followed by a registered letter if the responsible clinician cannot be contacted. Typographic errors and lack of clarity during transcription and dictation may also lead to significant errors. For example, failure to include the word "no" makes all of the difference between "there is evidence of malignancy" and "there is **no** evidence of malignancy". Lack of understanding of reports by clinicians, either due to the use of confusing terminologies or new classification systems, can also be a source of error.

The analytic phase of the testing cycle in anatomic pathology potentially can include both misdiagnoses and reports that are lacking in information that may be critical for treatment planning and prognostic assessment. Secondary (retrospective) case reviews form a crucial part of quality assurance programs of virtually all surgical pathology and cytopathology laboratories. This process includes a number of elements such as retrospective random reviews of a subset of all surgical pathology cases, reviews of a proportion (10%) of negative Pap smears, reviews of cases that are presented at subspecialty conferences and tumor boards, reviews of cases that are sent to other institutions when patients seek second clinical opinions and cases that are reviewed internally by other pathologists at daily departmental consensus conferences designed for the review of difficult or unusual cases. Most of these approaches

involve retrospective reviews, but many departments also employ prospective reviews of all newly diagnosed malignancies or subsets of particularly problematic biopsy types. For example, some pathology departments require that two pathologists review prostate and breast biopsies prior to signout. Quality assurance tools of this type can reduce diagnostic errors in the analytic phase significantly.

Estimates of error rates in surgical pathology and cytopathology have been difficult to obtain. In a study of more than 6,000 biopsies subjected to mandatory secondary opinion, Kronz and coworkers¹⁶ reported a changed diagnosis (error) in 1.4% of cases. Errors in this study were defined as those events requiring a major modification in therapy or prognosis. Biopsies most likely to undergo a significant diagnostic change included those from serosal membranes (9.5%) and female reproductive system (5.1%). In a more recent analysis of errors from multiple laboratories, the mean surgical pathology discrepancy rate was 6.8% while the mean cytology discrepancy rate was 6.7%.¹⁷ Additional failure points in the analytic phase include failure to review prior biopsy and cytological specimens and review of incorrect slides as a result of mixups of the accompanying paperwork.

Inter-observer variability in diagnostic interpretation is a well-known problem in surgical pathology for certain organ systems and disease processes (e.g. classification of melanocytic lesions of the skin, distinction of atypical hyperplasia of the breast from low grade *in situ* ductal carcinomas).^{18,19} Attempts to develop and apply standardized and generally accepted criteria are underway in many of these areas of diagnostic uncertainty and they have begun to result in lower discrepancy rates.²⁰ As noted by Renshaw, many differences in diagnostic threshold are not verifiable and the generally accepted opinion for malignancy is not 100% specific when follow-up material is used as the gold standard.¹¹

The US Congress passed CLIA-88 as an answer to diagnostic inadequacies

of gynecologic cytology reported in the media. The participation in a proficiency testing program mandated by CLIA-88 is limited to gynecologic cytology; it took almost 16 years to implement the program. By June of 2005 all laboratories performing gynecologic cytology must be enrolled in an approved proficiency testing program. There is no current requirement for mandatory proficiency testing in surgical pathology although many laboratories subscribe to voluntary proficiency testing programs.

The CAP requires that all accredited surgical pathology services participate in a peer educational program. The CAP offers numerous educational and quality management programs including The Performance Improvement Program (PIP) in Surgical Pathology, Interlaboratory Comparison Program in Non-Gynecologic Cytopathology and Cervicovaginal Cytopathology, and the Q-Probes and Q-Tracts which are quality management tools. The programs offer peer comparison data and an educational critique. Laboratories participating in these programs can use the data to benchmark their performance and compare it with participating peers.

RESPONSE TO THE IOM REPORT

The IOM report served as a springboard for many initiatives, including:

- The formation of the **Agency of Healthcare Research and Quality (AHRQ)** with the purpose of improving the quality, safety, efficiency and effectiveness of healthcare for all Americans.
- The **Centers for Disease Control and Prevention (CDC)** have promoted and supported the creation of the **Institute of Quality in Laboratory Medicine (IQLM)** with the purpose of improving healthcare through quality laboratory services. There are 40 partner organizations including CAP, JCAHO, COLA, FDA, AMA, Blue Cross and Blue Shield Association, Federation of American Hospitals, Clinical and

Laboratory Standards Institute and others. <http://www.phppo.cdc.gov/dls/iqlm/> Accessed January 29, 2005.

- The Leapfrog Group was created by 160 companies who purchase healthcare services with the purpose of reducing preventable medical errors, improving the quality and affordability of healthcare and encouraging public reporting of healthcare quality and outcomes to enable consumers to make more informed choices. <http://www.leapfroggroup.org/about.htm> Accessed February 10, 2005.
- At the University of Pittsburgh, members of the Department of Pathology have established a Center of Excellence in Pathology Quality and Healthcare Research.²¹
- The US government and President George W. Bush have been promoting the adoption of the electronic medical record and universal interconnectivity as a major safety initiative. This requires standardization of information methods that at present are lacking. Furthermore, the **Logical Observation Identifier Names and Codes (LOINC)** is a universal code system that provides a common context for clinical and laboratory variables. Regrettably, few vendors offer this method at present.

The US House of Representatives and Senate each passed patient safety legislation in the 108th Congress.²² In March, 2003, the House passed the Patient Safety and Quality Improvement Act (H.R.663) by a vote of 418 to 6; the Senate passed its version of the legislation in July, 2004, by unanimous consent. Before becoming law, the House and Senate versions of the legislation must be reconciled before approval and signature by the President. The Act seeks to create a confidential voluntary reporting system in which physicians, hospitals and healthcare providers could report information on errors to patient safety

organizations. The patient safety organizations would then collect and analyze the data to devise patient safety improvement strategies. Differences between the House and Senate versions of the bills relate to the scope of confidentiality, certification of patient safety organizations and the definition of patient safety information.²²

Twenty states, including Rhode Island, have enacted some form of medical error reporting law. Only Pennsylvania has a comprehensive medical error reporting system. Health care facilities are required to report not only serious events but also near misses and infrastructure failures (e.g. power failures). In addition, the newly created Patient Safety Authority is charged with identifying patient safety issues and recommending solutions.²³

Are we on the right path to reduce human error? Is it possible to reduce human error? Hollensead et al⁸ said it best: "Reduction of human error through root-cause analysis, process control, enhanced metric utilization, use of newer information technologies, and constant education and communication can be achieved." We say amen to that.

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BENEFITS OF LABORATORY AUTOMATION: SAFETY AND ACCURACY

DAVID J MORRIS, PHD, AND STEVEN SMEAL, MS, MT (ASCP)

With improvements in analytical technology and laboratory information systems over the past decade, novel approaches to manage the workflow of highly complex laboratory operations more efficiently are being evaluated. (Figure 1) The challenge is to accommodate the increased workload while lowering the unit cost of performing the testing, especially in light of lower reimbursement rates. Inevitably, laboratory automation emerges as a potential solution.



Figure 1: Rhode Island Hospital Laboratory (Early 20th century).

The typical scenario occurs when the laboratory begins to search for a more current methodology and instrumentation to replace outdated analyzers with the goal of having larger menu-driven systems, with faster throughput, which can aid in the consolidation of workstations. For example, an instrument could be chosen which could perform multiple therapeutic drug levels simultaneously, rather than performing the assays on several pieces of equipment. This leads to the possibility of considering the components of the latest generation of equipment which can automate many pre- and post-analyti-

cal functions. Pre-analytical functions include confirmation of sample receipt and positive-sample identification, centrifugation and preparation and labeling of aliquots. Each of these steps is subject to human error if performed manually. Similarly, post-analytical functions including sorting, storage, labeling and retrieval, and electronic archiving, are also fraught with the same possibility of error.

At the same time, the laboratory is trying to maintain itself in a com-

petitive posture, searching for the best technologies and analytical methods while dealing with the shortage of skilled laboratory professionals. Additionally, the laboratory may be looking to increase revenues by launching or expanding an existing outreach program. In any event, these are the times to consider all possible solutions.

Having seen presentations demonstrating that automation of laboratory systems is taking place in the US and throughout the world at an increasing pace, what are the reasons and justifications for choosing laboratory automation over traditional labora-

tory operations? What benefits can be accrued by automation? Will it reduce pre- and post-analytical errors in handling of specimens and reduce test **turnaround times (TATs)**? What automation components should be considered to achieve these goals? Will automation help to handle the increasing volumes and shortages of personnel? Will laboratory automation make the laboratory safer?

RATIONALES FOR INTRODUCING A LABORATORY AUTOMATION SYSTEM

The first images that probably flash across one's mind are computer downtimes, power outages, equipment failures, service issues, and crises when the system is down, all too horrific to contemplate. Then there is the cost. In times of fiscal and capital restraint, it is difficult to believe that any laboratory would be in a position to acquire such "cutting edge" technology. However, since there are currently over 120 automated laboratory systems operating in the US, this approach must be feasible.¹

The automation system for our Biochemistry Laboratory has been in operation for nearly 4 years. The principle gains have been:

- **Accuracy of steps previously performed manually** – One of the major areas where the laboratory focused great attention in past years was the elimination of potential failure points in processes subject to errors. Bidirectional instrument interfaces have had a significant impact on these types of errors. However, failure points still exist. These include all pre-analytical steps including the manual creation of aliquot tubes which can result not only in sample mis-identification but also cross contamination of specimens. For the traditional laboratory, up to 12 sets of hands could handle a specimen from the time it is drawn to

the time the testing is completed and reported; automation could reduce this handling by more than 50%. Automation of all pre-analytical steps including an automated aliquotter provides 100% accuracy, as well as positive sample identification with no cross-contamination of samples.

- **Safety concerns for staff** – Automation eliminates much of the direct handling of specimens including removal of caps, centrifugation, the creation of aliquot tubes and the recapping of samples. Clearly, laboratory automation circumvents exposure of laboratory staff to potentially hazardous samples.²⁻⁴
- **Faster throughput of specimens** – Automation never gets distracted or forgets about the sample in the centrifuge. In the traditional laboratory, there are many steps where a technologist must simply move a sample from one station to another. Each step, be it placing or removing a sample from a centrifuge to loading the sample onto an analyzer, can introduce delays in TAT for result reporting. Automation is constant, effortless and 100% reliable.⁵
- **Retrieval of specimens** – A good deal of technologist time is spent each day locating samples for “add on” requests or for additional testing at another workstation. With an automated refrigerator stockyard and a few keystrokes the line automation can be instructed to retrieve a sample, remove the cap and send it to the appropriate workstation for analysis without the technologist leaving his/her seat, with 100% safety and accuracy.²⁻⁴
- **Morale boost** for staff to belong to a lab at the cutting edge of technology. Additionally, automation will serve as a recruitment and retention enhancer attracting highly qualified laboratory professionals, seeking a change or a new challenge.⁴
- **Provision of adequate time** for the development of new testing strategies and total quality management parameters.

BENEFITS

Consolidation of testing performed on several instruments onto a single more efficient analyzer is a potent financial benefit. In fact, the selection of the correct analyzer may do more to save money than the automation itself in some cases. Additionally, many new analyzers utilize cap-piercing methodologies which permit sampling of specimens without removal of caps from vacutainers. They may also permit automation of procedures which had been done manually, and allow for “on board dilution” and “automatic repeat functions” at certain programmable levels. These features not only enhance technologist safety but also improve overall accuracy of specimen identification and performance of assays.²⁻⁴

Implementation of auto-verification permits a laboratory to release results automatically on patients with normal or near normal values. This step markedly improves TATs, permitting the technologist to spend more time on those problematic samples with highly abnormal results.

OVERVIEW OF LABORATORY AUTOMATION COMPONENTS

Having successfully deployed new chemistry analyzers and implemented a large laboratory automation system successfully, we would like to review the components chosen and their roles and functionalities. (Figures 2-6) In the Fall of 2001, the Core Laboratory of Lifespan Laboratories went live with a Beckman Laboratory Automation (Robotic) system. This

system fully automates a large portion of the Biochemistry Laboratory which currently performs approximately 1.6M assays/yr. (1,600 tubes/day). The system includes the following components:

- Inlet or sample loading area providing the opportunity to load 200 samples simultaneously
- Centrifuge equipped with robotic arms which can load, spin, and unload up to 40 samples at a time
- Clot Level Detector using infrared light (used in conjunction with the Aliquotter for Clinical Immunology specimens)
- Decapper which automatically removes and discards the caps on samples
- Aliquotter which uses disposable tips, to prevent contamination of samples and a bar code printer to generate labels identical to the original label
- 2 Beckman LX-20 Chemistry analyzers connected to the line
- Bayer Centaur Immunochemistry analyzer connected to the line,
- Recapper which caps all original tubes and aliquot tubes robotically prepared.
- Refrigerated stockyard, connected to the line, which stores 3060 primary tubes
- Retrieval Decapper which removes caps from tubes coming out of the Refrigerated Stockyard for additional testing
- An outlet with several storage racks at the end of the line which sorts primary and aliquotted Clinical Immunology specimens.

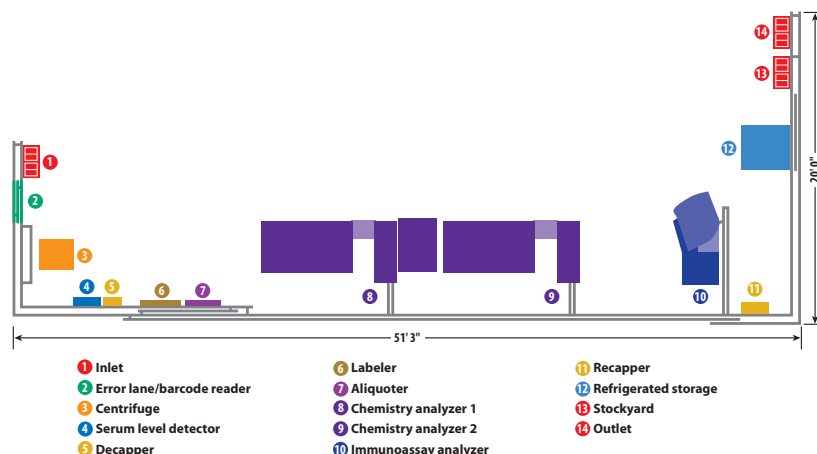


Figure 2: Schematic of operational flow for the laboratory automation system at The Miriam Hospital.



Figure 3: Robotic line from the laboratory automation system at The Miriam Hospital



Figure 4: Specimens ready to be placed on robotic line.



Figure 5: Robotic fingers placing specimens on robotic line.



Figure 6: Laser based barcode-driven sorting for clinical immunology testing.

KEY STEPS TAKEN

Many decisions were made prior to implementing the automated laboratory system. Some of the early decisions included:

- **Barcodes:** The barcode contains all relevant information which links the sample to the patient information and the specific tests ordered. The barcode label can be tracked throughout all phases of the testing and storage processes.
- **Sample Requirements:** All specimens received at the Core Laboratory from affiliated hospitals, outreach sites, clinics and floors at each Hospital, were required to meet the following specifications, where feasible:

- Standardized tube size. Robotics optimally functions with a single sized tube.
- Use of plastic tubes. This was performed in order to avoid breakage in the centrifuge or refrigerated stockyard
- Barcodes. Standardized so that all samples arrived in the laboratory Barcode labeled whenever possible.
- Nurse Order Entry. Nurse Order Entry was on-board at all affiliated hospitals prior to initiation of laboratory automation. This was one of the most important considerations in the streamlining of pre-analytical functions prior to automation.
- **Laboratory Automation Support Personnel.** A group of technologists was trained to troubleshoot and

perform routine maintenance on the line automation. This was essential to the success of the automated laboratory.

OPERATIONAL FLOW OF LABORATORY AUTOMATION (FIGURES 3-6)

- Barcode labeled tubes are placed robotically on the line, where the first Barcode reader wands them, thereby bringing them to an "In Lab" status and verifying that an order has been downloaded through an interface. All physicians' orders are electronically transmitted from the Order Entry computer through an interface to the analyzer which then "knows" which tests to perform on any given sample. (All results from the analyzer are ultimately transmitted through the same interface to the Hospital Information System and are immediately available in the patient record.)
- Tubes are automatically loaded into the centrifuge, balanced, if necessary, and spun for four minutes. They are then replaced robotically on the line. An Infrared Level sensor measures the height of the red blood clot. The sample caps are then removed and discarded, thereby eliminating the risk associated with the production of aerosols.
- Clinical Immunology tubes are aliquotted (with disposable tips) into daughter tubes which have been identically barcode labeled. The parent tube, followed by the daughter tube(s) pass down the line, recapped, and sorted at an ambient outlet at the end of line into designated workstation locations. This process is 100% accurate and eliminates the exposure of technologists when preparing manual aliquots and the attendant mis-identification of specimens.
- Primary Chemistry tubes are loaded robotically onto two LX-20s, with identical test menus. This allows one system to be taken "off line" for maintenance while the second can handle any samples that are loaded. These analyzers perform most "routine" chemistry assays on serum, urine, and CSF, including

therapeutic drug monitoring

- Samples directed to the track- ready Bayer Centaur Immunochemistry Analyzer are checked 3 times by separate barcode readers to ensure positive sample identification prior to analysis. The Centaur samples specimens using disposable tips, directly from the line automation, eliminating sample carry-over. These steps ensure 100% accuracy and safety of all procedural steps. This analyzer measures cardiac markers, cancer markers, and many endocrinology assays
- All tubes, after sampling, are recapped and removed robotically from the line and stored in a refrigerated stockyard, holding up to 3,060 tubes. During this time when a clinician requests an "Add-on" on either the LX-20's or the Bayer Centaur, the required tube is automatically retrieved from refrigerated stockyard in less than 15 seconds and placed back on the line for analysis. This process, similar to the aliquotting process, is 100% accurate and reduces exposure of technologists to hazardous specimens. An initial result for any specimen, Stat or Routine, is obtained within 20-45 minutes of being placed on the line, depending on the test mix ordered.
- The DataLink 2000 which handles all results and indices (hemolysis, lipemia, and bilirubin) from the Beckman LX-20 permits efficient auto-verification. It also permits all STAT tubes placed on the Line to be expeditiously handled, leading to an additional decrease in TATs for these critical samples.

CONCLUSIONS

Within the next 2-5 years, many directors of clinical laboratories throughout the US will implement various automation components. This is undoubtedly the "way to go". We have found that automation has led to a marked and consistent improvement in the TATs of all routine and STAT samples and has provided physicians with a broad menu of biochemistry tests 24 hours per day. When justifying the implementation of laboratory

automation, not only cost savings (both FTEs and reagents) and efficiency need to be highlighted but also gains in patient and laboratory safety and accuracy. Over time the improved ability to accurately identify and retrieve specimens safely for additional testing will be seen as one of the major features gained by automation. Automation offers the opportunity to transform a traditionally operated laboratory into a modern, safe and very clinician-friendly environment.

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- [Figures 3-6 Reprinted from *Clinical Laboratory News*, December 2004. Used with permission of the American Association for Clinical Chemistry, Washington, D.C.]

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RESIDUAL RISKS OF BLOOD TRANSFUSION IN RHODE ISLAND

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Landsteiner's¹ 1900 discovery of the ABO blood group system was the pivotal observation that overcame the major obstacle to blood transfusion; i.e., the prevention of an acute hemolytic transfusion reaction. Despite this, testing for ABO system compatibility did not become common practice for several years.²⁻⁴ In the subsequent five decades (1910-1960), most of the blood group systems were described, together with the most common antigens associated with specific alloantibody formation. Concurrent with these findings, pretransfusion compatibility testing evolved and routine testing for ABO antigens and antibodies, determination of Rh(D) status and performance of an indirect antiglobulin test, became standard. Although earlier techniques used capillary tubes and slides, tube-testing subsequently became standard. All these techniques were, and continue to be, performed manually by laboratory technologists. These manual techniques, however, are prone to both clerical and technical errors. Automated techniques using gel agglutination technology or microtitre plates have recently been introduced into hospital blood banks. The prevention of hemolytic transfusion reactions still remains the major objective and, in this regard, considerable success has been achieved. Estimates are that an incompatible transfusion resulting in an acute hemolytic transfusion reaction occurs with a frequency of approximately 1:100,000 and a fatal hemolytic transfusion reaction with a frequency of less than 1:1,500,000.⁵ In most instances, the cause is a clerical error, not a technical failure.^{6,7}

The latter decades of the 20th century became equally focused on the transmission of disease by blood transfusion, particularly syphilis and hepatitis viruses.⁸ Testing for these microbes was introduced in 1948 and 1972 respectively. Since then many

more tests have been implemented to interdict other pathogens. The chronology is shown in Table 1. The earlier tests used agglutination techniques, but radiometric tests came into use in the 1970s, to be replaced by ELISA tests in the 1980s. In the 1990s, nucleic acid testing became available to detect HCV and HIV-1 genome, and this technique was also used to detect **West Nile Virus (WNV)**.^{9,10} In 2004, bacterial culturing of all platelet products was achieved in Rhode Island, with the expectation that this will greatly reduce the likelihood of bacterial sepsis. Thus, by early 2005, assuming a 1-2-log (95%) reduction in bacterial sepsis (from 1:4,000 – <1:200,000), the likelihood of any viral or bacterial disease transmission by blood transmission is about 1:150,000 and this is likely to be HBV,¹⁰ but emerging pathogens, such as SARS virus, influenza virus and prions, remain a concern.

The years 1900 – 2000 saw dramatic reduction in both the risk of a hemolytic transfusion reaction and of infectious disease transmission, but other complications became

evident. Foremost is the occurrence of **Transfusion Related Acute Lung Injury (TRALI)**, in which transfusion recipients develop acute onset non-cardiogenic pulmonary edema. Other rare complications include **Transfusion Associated Graft Versus Host Disease (TA-GVHD)**, **Post Transfusion Purpura (PTP)** transfusion induced fluid overload, hyperkalemia, hypocalcemia or hemosiderosis. (Table 2)

The most common reactions observed (0.22%) are minor allergic reactions (urticaria) or inflammatory type reactions (non hemolytic febrile transfusion reactions). Both are usually clinically mild and transient, rarely lasting more than 45 minutes. Allergic reactions respond to slowing the transfusion or administration of an antihistamine, and inflammatory type reactions respond to acetaminophen, but routine prophylactic use of these should be discouraged.^{11, 12} The frequency of the latter type reaction has been significantly reduced by universal leukoreduction.¹³⁻¹⁵ The pathophysiology of these reactions is reasonably well understood and they

Table 1

Chronology of Test Implementation to Interdict Microbial Transmission by Blood Transfusion

| * Surrogate tests | † Discontinued with NAT HIV-1 Testing |
|-------------------------------|---------------------------------------|
| Syphilis | 1948 |
| HBV:Ag | 1972 |
| Anti-HIV-1 | 1985 |
| Anti HCV | 1986* |
| ALT Level | 1986* |
| Anti-HTLV-1 | 1988 |
| Anti-HCV | 1990 |
| Anti HIV 1/2 | 1992 |
| p24 Antigen | 1996† |
| NAT: HIV-1 | 1999 |
| NAT: HCV | 1999 |
| NAT: WNV | 2003 |
| Bacterial Culture (platelets) | 2004 |

NAT (Nucleic Acid Amplification Technology)

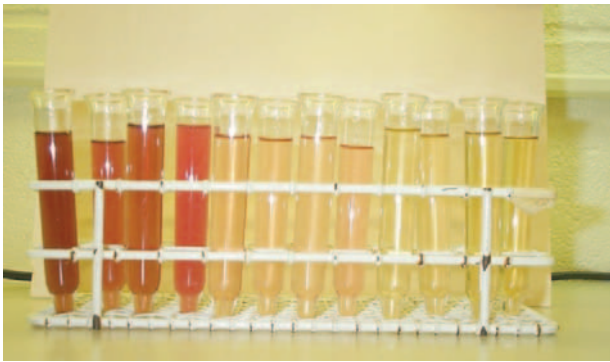


Figure 1: Acute Intravascular Hemolysis. Most cases are due to clerical errors. Hemoglobinemia and hemoglobinuria are characteristic; the latter usually clears within 6-12 hours.

will not be further discussed.^{16, 17}

I. IMMUNOLOGICALLY MEDIATED (A) ACUTE HEMOLYTIC TRANSFUSION REACTIONS (AHTR)

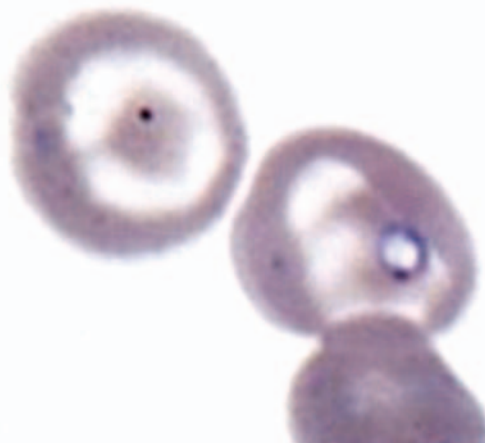
The residual risk of an acute HTR is difficult to estimate, but is approximately 1:50,000 – 1:100,000. (Figure1)¹⁸ The occurrence of an AHTR generally indicates a failure of compatibility testing and the points of failure are summarized in Table 3. Miscollected specimens are specimens in which the blood in the container is NOT that of the person whose name appears on the container label. Miscollected specimens need to be distinguished from mislabeled specimens. In the latter case, the labeling is incomplete or inconsistent, the error recognized by the Blood Bank and the specimen rejected. Miscollected specimens are of greater concern because they appear to be correctly labeled and, thus, accepted for processing. Miscollected specimens have an alarmingly observed prevalence of about 1:2,000 but the actual prevalence may be even higher, possibly 1:500 – 1:1,000.¹⁹ Mislabeled specimens are also about 10 times more likely to be also miscollected and, hence, a rigid policy to reject all mislabeled specimens is justified.²⁰ Miscollected specimens occur because of a failure to conform to written procedure in sample collection.²¹⁻²³ The most common error is that the sample is collected into a prelabeled container (where the label is not correct) or that the sample is collected into an unlabeled container and the labeling process occurs at a site other than the bedside, such as the

Nursing Station. Insistence on a

policy of collecting the sample into an unlabeled container with completion of the labeling process at the bedside would largely eliminate this error, but this appears difficult to enforce universally in practice. On account of this, technologies which allow bedside label generation with both clinical and electronic identification of the patient are increasingly being considered and most blood bank software vendors offer those systems as a safety feature. It seems likely that such systems will become the standard of care within the next decade.

Clerical or technical errors within the blood bank are a less common cause

Figure 3: Transfusion Transmitted Babesiosis. This is the most common microbe transmitted by blood transfusion in Rhode Island



of hemolytic transfusion reactions. These errors are attributable mainly to the multiple manual steps involved in test performance and manual data recording, either on paper or computer entry.^{19,22} Approaches to minimize these errors will involve automation of compatibility testing with electronic transfer of information from the testing device to the Blood Bank Information System through an approved interface. Many Blood Banks are now in the early phases of automation. Dispensing errors represent further challenges that are difficult to interdict. These errors occur despite the computerization of this step in most blood banks.



Figure 2: TRALI in a 25 Year Old Male after transfusion of plasma. Dyspnea commenced within one hour, with O_2 saturation of 50% on room air. Chest X-ray shows bilateral pulmonary edema.

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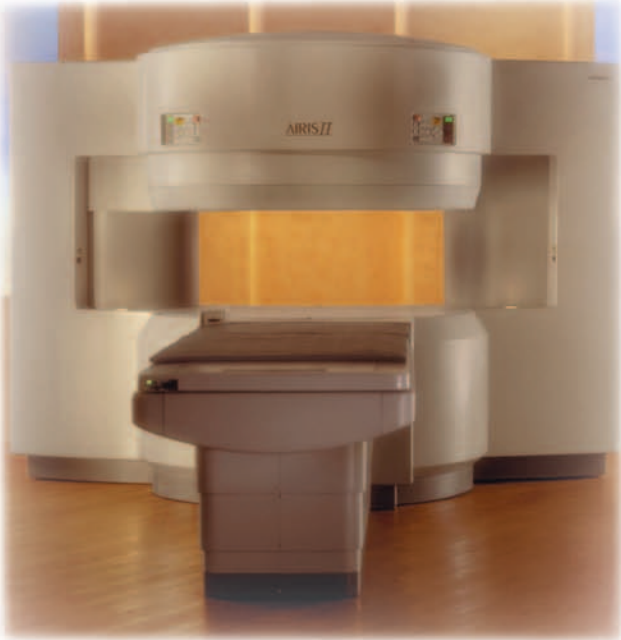
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Approaches to error minimalization at this failure point will likely focus on robotic dispensing devices, which have the added attractive feature of being capable of location in areas of high product use, such as the OR, and ICU. Finally, misadministration of the blood product still occurs when there is non-conformance with the written procedure.²⁴ The most common error here is that some of the confirmatory steps are performed at a site other than the bedside (such as the Nursing station) by two identifiers but only one identifier actually goes to the bedside to complete the identification. Insistence that all identification confirmation steps occur at the bedside by two personnel (transfusionist and co-identifier) would eliminate this error, but this appears also difficult to universally implement. The development of bar coded ID bands and the use of bar code readers by the transfusion personnel will be important advances in minimizing errors in patient misadministration. In this schema, identification is confirmed clerically and electronically. Such systems will also be used for medication administration and will likely become standard within a few years.^{25, 26, 27}

(B) TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)

TRALI is considered to be a frequently unrecognized complication of blood transfusion.²⁸ TRALI has been causally associated with all blood components, but occurs more frequently with plasma or components containing large amounts of plasma, such as platelets. The pathophysiology of TRALI is most probably due to antileukocyte antibodies in the plasma of the component, which react with recipient neutrophils,²⁹ but other mechanisms are also possible.³⁰ Binding of these alloantibodies results in complement fixation and the local generation of C5a and C3a in the first capillary plexus encountered, which is the lung. C5a causes neutrophil aggregation and chemotaxis and both C5a and C3a provoke an inflammatory process (alveolitis). Dyspnea is the most common clinical feature, but fever and chills may also occur. Chest X-ray shows bilateral pulmonary edema. (Figure 2) Treatment is largely symptomatic (oxygenation with/without ventilation) and full recovery occurs in the majority of patients (~85%) within 24-72 hours. A small minority do not recover; however, and TRALI is now considered the most common cause of acute death from blood transfusion, surpassing acute hemolytic reactions and bacterial sepsis from platelet transfusions.

Attempts to prevent/eliminate TRALI present logistic difficulties. Testing all plasma or platelet donors for HLA antibodies could prevent some cases, but at substantial cost and product loss. Of particular concern would be the loss of apheresis donors. Similarly, a policy to produce only red cell products from multiparous females could be helpful, but is of uncertain benefit. Alternative solutions could be plasma removal and re-suspension of platelets in additive solution, although none are licensed within the U.S. at present. Therefore, it is likely that this complication will remain for sometime with the actual risk in Rhode Island uncertain but may be in the range of 1:5,000.

(C) ANAPHYLAXIS

Anaphylaxis appears a very rare complication of blood transfusion and may have a frequency of 1:200,000 or less. In some cases (minority), this complication is due to IgG-anti IgA antibodies in sensitized IgA deficient recipients.³¹ The recipient must have undetectable IgA. Known IgA deficient recipients should receive plasma components from IgA deficient donors and cellular components should be either washed three times to remove the suspending fluid or from IgA deficient donors. Frozen deglycerolized red

| |
|---|
| <p>Table 2 Residual Risks of Severe Transfusion Related Adverse Events in Rhode Island</p> <p>I. Immunologically Mediated</p> <ul style="list-style-type: none"> A Hemolytic Transfusion Reaction B Transfusion Related Acute Lung Injury (TRALI) C Anaphylaxis D Post-Transfusion Purpura (PTP) E Transfusion Associated Graft Versus Host Disease (TA-GVHD) F Critical Organ Harm Attributable to Red Cell Storage (CHARS) <p>II. Non-Immunologically Mediated</p> <ul style="list-style-type: none"> A Microbes: <ul style="list-style-type: none"> 1 Protozoa: <i>M. bancrofti</i>, <i>T. cruzi</i>, <i>P. malaria</i>, <i>T. gondii</i> 2 Viruses: HBV, WNV, B19 parvovirus 3 Bacteria: Gram negatives in red cell sepsis (<i>Y. enterocolitica</i>, <i>S. liquefaciens</i>) 4 Prions: nv CJD B Fluid Overload and Metabolic Complications: <ul style="list-style-type: none"> 1 Transfusion Associated Circulatory Overload (TACO) 2 Hyperkalemia 3 Hypocalcemia 4 Hemosiderosis |
|---|

cells are preferred because of the solute removal during deglycerolization

(D) POST TRANSFUSION PURPURA (PTP)

Post transfusion purpura is a very rare complication of red cell or platelet transfusion occurring 7-14 days after transfusion in which the patient presents with thrombocytopenia associated bleeding and purpura.³² The thrombocytopenia is usually profound ($< 10 \times 10^9/L$). The pathophysiology is complex with most patients exhibiting a platelet alloantibody (anti HPA-1a, formerly PL^{A1}) in their serum/plasma (approximately 2% of the Caucasian population are HPA-1a negative, and hence at risk). The mechanism by which the transfusion induced alloantibody causes destruction of autologous (recipient) platelets which are antigen negative is unclear, but probably involves an 'innocent bystander' mechanism. These patients respond promptly to IVIG and steroids; plasma exchange can also be used. Mortality is rare, fortunately. These patients are generally advised to receive future transfusions as washed cells or components from HPA-1a negative donors.³³

(E) TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)

TA-GVHD is an extremely rare complication of cellular blood transfusion in which transfused viable allogeneic T-lymphocytes multiply and destroy (reject) host tissues.³⁴

GVHD involves skin, liver and the gastrointestinal tract. TA-GVHD differs from bone marrow transplant associated GVHD in that the host marrow is also involved, resulting in pancytopenia. Clinical features, such as skin rash, typically occur 2-3 weeks post transfusion. Nearly all cases are fatal. On account of this, susceptible recipients (T-cell immunocompromized) and products at risk (such as HLA matched platelets or directed donor blood from genetically related donor), are gamma irradiated. The residual risk for this complication in RI is likely to be less than 1:1,000,000.

(F) CRITICAL ORGAN HARM

ATTRIBUTABLE TO RED CELL STORAGE (CHARS)

CHARS is a newer area of investigation. It is clear that stored red cells undergo storage related changes which are potentially deleterious to the recipient, particularly ill recipients in the ICU setting. The transfusion of red cells stored in excess of 21 days appears to put these patients at increased risk for mortality. The mechanism is unknown, but red cell microvesiculation or accumulation of lipid material in the red cell supernatant could cause unintended and deleterious macrophage activation.³⁵⁻³⁹

II. NON-IMMUNOLOGICALLY MEDIATED

(A) MICROBES

(I) PROTOZOA

Babesia microti is likely the most common microbial disease transmitted by blood transfusion in Rhode Island. (Figure 3) *Babesia* species are endemic in Southern New England, upper mid-West and Northeast and are transmitted by tick bites, predominantly, but not exclusively from *Ixodes scapularis* (also known as *dammini*).⁴⁰ A phase of donor parasitemia ensues, but most infected subjects remain asymptomatic. Blood donated during parasitemia is contaminated and can cause infection in the transfusion recipient. However, most transfusion recipients are immunocompetent and symptomatic disease does not result. Immunocompromised or asplenic recipients, however, will develop symptomatic disease and require antiprotozoal therapy and sometimes

red cell exchange.

Interdicting the transmission of Babesiosis by blood transfusion is not simple. A history of tick bites is frequently given by donors in the Summer and early Fall, but most are not at risk for Babesial transmission. Furthermore, donors implicated in Babesial transmission often fail to remember a tick bite. Testing for antibody to microti would exclude large numbers of healthy donors and may also not interdict the early phase infected donors.⁴¹ Blood smear examination would also be unlikely to detect the very low level of parasitemia ($< 0.1\%$) in the asymptomatic donor. Perhaps nucleic acid testing to detect Babesial genome applied during the vulnerable early summer to fall period could be useful, but such tests are neither standardized nor FDA approved at present. The residual risk for infection transmission in Rhode Island is unknown, but based on data from Connecticut, may be as high as 1:600 red cells,⁴² but for clinical overt disease, 1:60,000. *Trypanosomiasis Cruzi* (Chagas's Disease) has been long known to be transmitted by blood transfusion, but most cases were reported in the Southwest, Florida or New York,⁴³ areas which have substantial numbers of immigrants from South and Central America. One case of transfusion transmission has occurred in Rhode Island. Unlike Babesiosis, donors at risk for *T. cruzi*, transmission can be screened using an antibody test, but the success of this is unclear. A more recent development of a test for Chagas's Disease may greatly facilitate the

Table 3

Potential Points of Failure in Compatibility Testing

1. Sample Collection: Misidentification of The Potential Recipient (Miscolected Specimen).
2. Clerical or Technical Error in the Transfusion Service.
 - Mislabeling of sample/tubes.
 - Technical errors.
 - Clerical errors.
 - Wrong product dispensing.
3. Administration of Blood Products.
 - Recipient misidentification.

detection of this microbe in the future.⁴⁴ The risk of malarial transmission (mostly *P. malariae*) or Toxoplasmosis (*T. gondii*) is considered extremely low at the present time.⁴⁵

(2) VIRUSES

Interdiction of the transmission of viral disease by blood transfusion has been one of the greater successes of the last two decades. The residual risk of transmitting any viral disease, which results in patient morbidity, is in the order of 1:150,000 and the most likely virus in this case is HBV. The residual risk of HCV is approximately 1:900,000 and HIV, approximately 1:1,500,000. Other viruses, such as CMV and B19 parvovirus, may be transmitted by blood transfusion, but clinical disease in the recipient may not be evident. The policy of universal leukoreduction has eliminated almost all CMV transmission (and likely HTLV-I/II).¹⁵ Application of NAT testing of each donation for HBV may even further reduce this already very low risk.⁴⁶⁻⁴⁹

(3) BACTERIA

Most reported cases of bacterial sepsis caused by blood transfusion involved platelet products.⁵⁰ In October 2003, Rhode Island commenced testing platelets for bacterial contamination; by February 2004, all platelet products were tested prior to shipping to hospital transfusion services. Although it is unclear how many cases are interdicted, it is likely that 90-95% of infected products will be identified. Since the risk of platelet associated bacterial sepsis was estimated at 1:4,000 transfusions, a 90-95% reduction would leave the residual risk of this complication at approximately 1:200,000. Red cell sepsis is estimated in the US at 1:500,000 units. Most cases are due to *Y. enterocolitica* or more recently *S. liquefaciens*. Universal prestorage leukoreduction reduces the likelihood of the former.⁵¹ As Rhode Island transfuses about 60,000 units RBC per year and 6,000 platelet doses, about 1 case of red cell sepsis will occur in 10 years and 1 case of platelet sepsis in 15 years.

(4) PRIONS

There is considerable recent interest in the transmission of prion diseases by blood transfusion.⁵² Prion disease is caused by an abnormal form of a protein termed PrP^{scn} or PrP^C, which is a normal constituent of the neurons in the central nervous system and is also expressed on the surface membrane of B lymphocytes. The abnormal form of this protein, designated PrP^{Sc} or PrP^{Res}, is resistant to protease digestion. The PrP^{Sc} form resembles the normal protein PrP^C, except that the PrP^{Sc} protein is more unfolded. Exposure of the normal PrP^C protein to the abnormal PrP^{Sc} protein causes the normal PrP^C protein to become unfolded, like the PrP^{Sc} protein, and excessive accumulation of the PrP^{Sc} protein then occurs with resulting cell death. Much of the attention has focused on Creutzfeldt-Jakob disease (CJD) with the recent demonstration that a new variant of CJD (nvCJD) is caused by the same prion which causes a disease in cattle called **bovine spongiform encephalopathy (BSE or Mad Cow Disease)**. The concern is that asymptomatic donors, who are incubating nvCJD, could have the prion particle in blood and could transmit this disease by blood donation. It was previously observed that B lymphocytes may be important in transporting this disease to the central nervous system in inoculated animals and this increased interest in providing leukoreduced blood for all transfusion recipients and has contributed to the recent decision by European countries and Canada to universally leukoreduce all cellular blood products. The demonstration that prion disease could be transmitted by blood transfusion from intraperitoneal inoculated sheep increased concern and in 2004, two cases of presumptive human-to-human transmitted nvCJD were reported in the U.K.^{53, 54} The risk of nvCJD transmission is extremely low in Rhode Island but is probably not zero. Recently, a commercial filter has become available which is capable of a 2-4 log reduction in prion protein in red cells and it may gain use in countries where prion disease transmission is of public concern, such as the UK, Ireland and France.

(B) FLUID OVERLOAD AND METABOLIC COMPLICATIONS

Transfusion Associated Circulatory Overload (TACO) should

always be suspected in a patient with a poor cardiac status or in an elderly decompensating patient receiving a blood transfusion. Acute hypervolemia will present as acute shortness of breath and distinguishing this from TRALI may be difficult. Intravenous diuretics will improve the situation rapidly in hypervolemia, but not in TRALI. If doubt exists, hemodynamic measurements will easily make the distinction. It is primarily to prevent acute hypervolemia that blood transfusions are administered over lengthy periods of time, sometimes up to 4 hours. This is largely unnecessary for the majority of blood transfusion recipients, however.

Acute metabolic abnormalities are seen only in association with massive transfusion. Hyperkalemia is seen in patients who are massively transfused with red blood cells.⁵⁵ This can particularly occur with red blood cells which have been irradiated, since the potassium levels in the supernatant of these products can be very high (60-90 mEq/L) or in a recipient who has a limited ability to accommodate to a high potassium challenge, such as an infant undergoing exchange transfusion or an adult patient with renal failure. Acute hypocalcemia may occur with the transfusion of large amounts of plasma containing products, particularly fresh frozen plasma and, to a lesser extent, platelets. These products are stored in citrate which is capable of calcium chelation. Ordinarily, transfused citrate will be metabolized rapidly to carbon dioxide, giving rise to the production of bicarbonate and a metabolic alkalosis. If the concentration of citrate delivered to the liver is excessive, acute hypocalcemia can occur with the clinical features of tetany, convulsions and hypotension. Routine transfusion of calcium gluconate to patients receiving only red cell transfusions has no basis since most red cells are stored in an additive solution, which does not contain citrate. In addition, a massive transfusion of plasma (1 unit every 5-10 minutes) is necessary

before this complication is likely to occur.⁵⁶ The administration of calcium should be restricted to the setting of massive transfusion, therefore, and calcium chloride is preferred, since it readily supplies ionized calcium. In practice, prophylactic calcium is only administered to patients undergoing therapeutic apheresis, particularly plasma exchange.

CONCLUSIONS

The risk per unit of any adverse event attributable to blood transfusion is approximately 1:500 and, in nearly all cases, the clinical reaction is transient (15-45 minutes). Although causing patient discomfort, the reaction is not life-threatening. Very rarely (< 1:50,000 units), a more severe reaction may occur, but even in these situations, mortality is uncommon (5-15%). Blood transfusion, therefore, when properly administered, is one of the safer therapeutic interventions in the hospital setting despite the common perception to the contrary. However, there is no room for complacency. Existing pathogens (such as SARS virus, prions and protozoa) and other hazards (TRALI, CHARS) will require the application of new testing, processing or storage technologies to abrogate, attenuate or eliminate the risk. In this regard, Rhode Island has been in the forefront; it was the first State to implement NAT testing for HIV-1 and HCV (1999), universal leukoreduction (2000) and universal testing for bacteria in all platelet products (2004). Although a zero risk blood supply is an unattainable goal, great strides have been achieved in this direction. The expectation is that Rhode Island will maintain its leading position in this regard.

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ADVANCES IN CYTOPATHOLOGY

SCOTT WANG, MD, AND LATHA PISHARODI, MD

The most significant success in the war against cancer was Dr. George Papanicolaou's introduction of the cervical/vaginal "Pap smear". The Pap smear detects the earliest precursor lesions of cervical cancer, so called **cervical intraepithelial neoplasia (CIN)**, which can be cured in virtually all cases if appropriately treated at this stage. Fortunately, the majority of these early lesions, which derive from precursor squamous cells present at the squamocolumnar junction at the entrance to the endocervical canal, exhibit cytologic abnormalities in the surface lining cells which can be detected microscopically and can be discriminated from normal lining cells by trained cytotechnologists and pathologists.

Prior to the late 1920s, cervical cancer was the leading cause of cancer death in women. With testing, death from cervical cancer in the United States decreased 70 to 80% in actively screened populations; it now represents the fourteenth most common cancer, accounting for less than 2% of the cancer deaths in women. Pap smear screening, however, is far from widespread: throughout the world cervical cancer is the third most common type of malignancy in women.

MONOLAYER TECHNOLOGY AND HPV TESTING IN PAP SMEARS

Although minor improvements were made in the years following the introduction of the "Pap smear" in the instruments used to collect cervical/vaginal lining cells, the stains used to highlight the differences between normal and atypical cells and the microscopes used to view these cells,

"REFLEX HPV TESTING HAS BEEN FOUND TO BE POSITIVE FOR HIGH RISK TYPE HPV IN ROUGHLY HALF OF THOSE PATIENTS DIAGNOSED AS ASCUS ON PAP SMEAR."

major technological changes did not occur until the 1990s. Until this time Pap smears were produced by smearing cells directly onto glass slides followed by immediate fixation. In May 1996 the liquid-based ThinPrep Pap Test, produced and marketed by Cytyc Corporation of Boxborough, MA,

became the first alternative technique approved by the **Food and Drug Administration (FDA)** as a significant improvement to the conventional cervical Pap smear. In 1999 the FDA approved a second liquid-based technology, SurePath, developed and marketed by the Tripath Corporation of Burlington, NC. Both these technologies utilize proprietary liquid fixatives into which cells obtained from the cervix are collected and prepared through various concentration methods into an easily viewable monolayer or thin layer preparation.

One may ask, "why replace a method which has already proved its merit for decades with newer more expensive technologies?"

There are several problems with the traditional "Pap" smear. First, is the problem with the transfer of cells from the collecting device, such as the Ayre spatula, endocervical brush or broom-type devices, to the glass slide. Studies have shown that the majority of the cells collected with these devices are discarded as waste along with the device and are not present for microscopic viewing.¹ In one study up to two thirds of false negative Pap smears were due to limitations in either sampling or slide preparation.² In another study sampling alone was a factor in up to 90% of the false negative smears.³ With the liquid-based technologies, all the collected

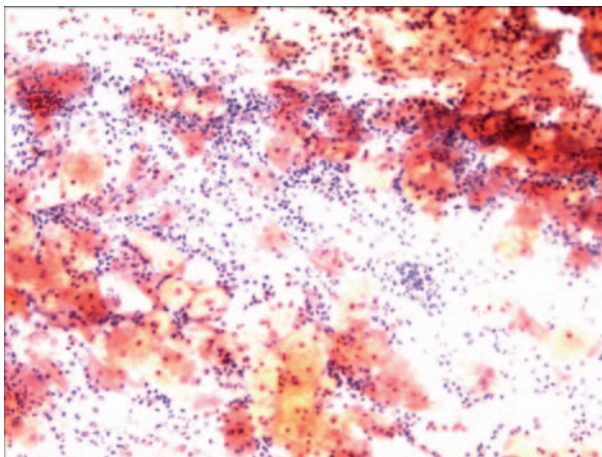


Figure 1: Conventional Pap smear showing squamous cells with obscuring inflammation, poor preservation of cells and a "dirty" background

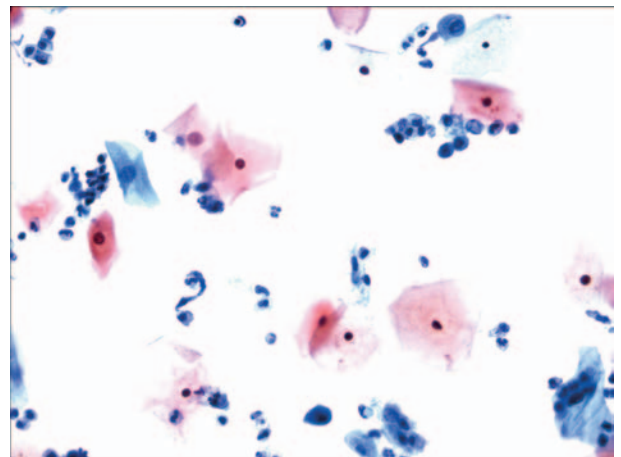


Figure 2: ThinPrep Pap smear showing well preserved benign squamous cells arranged in a monolayer in a clean background.

cells are present in the liquid fixative, even if only a fraction of the cells is evaluated microscopically. Both these technologies claim that the cells are mixed and randomly sampled in such a manner that one is assured of viewing a clinically significant proportion of the cells present, representative of the cells present on the surface of the cervix in the patient.

The second major advantage of the liquid-based technologies relates to improvement in the smear quality and the ability to assess cells without the frequent problems inherent to conventional Pap smears. For example, it is not uncommon to have many or most cells on conventional Pap smears either covered by piling up of the cells or by extraneous inflammatory cells, blood, mucus, debris or bacteria. (Figure 1) Up to 40% of all Pap smears may be compromised by these factors.⁴ The liquid-based technologies help to remove these obscuring factors and produce a thin monolayer of cells for viewing, although some degree of crowding still cannot be avoided. (Figure 2) Cytyc's ThinPrep Pap utilizes vacuum filtration across a thin membrane filter to isolate and concentrate cells, while Tripath's Surepath utilizes a density gradient centrifugation process to separate cells from obscuring debris.

Both Cytyc and Tripath, the competitors who developed and marketed the two main liquid-based technologies, had to prove that their systems were not only as good as but also provided a statistically significant improvement over the conventional Pap smear in the detection of cervical cancer and its main precursor lesions, the **squamous intraepithelial lesions (SILs)**. Both companies funded and published numerous studies performed in a variety of clinical settings to prove their claims. Key investigations involved comparisons of biopsy and colposcopically confirmed patient results to those obtained with either conventional Pap smears or concurrent liquid-based technologies. Cytyc has claimed that its ThinPrep Pap smear results in a 65% increased detection of precancerous lesions and a 59.7%

increase in the detection of high grade and more advanced lesions. Tripath has claimed that the SurePath instrument results in a nearly identical 64.4% increase in detection of high grade and more advanced lesions in comparison to the conventional Pap smear. Both technologies also report a decrease in the rate of smears previously classified as "satisfactory but limited by-" or "unsatisfactory", both of which are less than optimal readings frequently necessitating a repeat Pap smear or further studies. According to SurePath's promotional material, "10 to 30% of conventional Pap smears are considered limited, while 1 to 2% are unsatisfactory for evaluation." ThinPrep claims a 35% reduction in "satisfactory but limited by-" and a 73% reduction in the "unsatisfactory" category in comparison to the conventional Pap smear,⁵ while SurePath claims a 44% reduction in "satisfactory but limited by-" and a 39% reduction in "unsatisfactory". Both also claim that their products decrease the number of cases diagnosed as "**atypical squamous cells of undetermined significance**" (ASCUS), considered the gray zone between normal or reactive Pap smears and those with outright precancerous lesions or dysplasia. With increased experience, some investigators now also claim that the liquid-based technologies can even more accurately detect the less common and more diagnostically challenging glandular lesions of the endocervix, including adenocarcinoma in situ. The latter lesions comprise a larger group of the currently diagnosed cases of cervical cancer than in previous years.

Perhaps the most significant advantage of the liquid-based technologies is their ability to permit reexamination of cells in the collection vial to produce additional smears for viewing or for the performance of ancillary studies, including screening for sexually transmitted diseases. The most important of these ancillary tests are for the detection of low and high risk **Human Papilloma Virus (HPV)**. It has become clear that infection with one or more of the oncogenic types of HPV is a necessary precursor, if not the primary cause, of cervical

cancer and its precancerous stages.^{6,7} This parallels the known association of cervical cancer with the number of sexual partners and early onset of sexual activity since HPV is the most common sexually transmitted disease. Most HPV infections clear spontaneously within a year or two, but those that persist can lead to cervical cancer. Although most of the colposcopically and histologically evident precancerous lesions are detected with conventional and the improved liquid-based screening methodologies, recent estimates claim that even the liquid-based cytologic techniques may miss 5 to 35% of the high grade (CIN3) lesions or cervical cancers on routine screening.⁸ Testing for HPV increases the sensitivity for identifying these false-negative or missed high grade lesions up to 96% with a greater than 99% negative predictive value. This translates to the fact that there is a greater than 99% chance that a woman with a negative HPV test does not harbor a high grade precancerous lesion.⁹

Presently, the only FDA-approved HPV test is the Hybrid Capture 2 test produced and marketed by Digene Corporation of Gaithersburg, MD, for use with the ThinPrep Pap Test. The Hybrid Capture 2 HPV Test is a nucleic acid hybridization assay which utilizes RNA probes directed against either 13 high risk or 5 low risk HPV viral types. The high risk types are of most concern, since these are the viruses associated with the development of high grade CIN and cervical cancer. Since residual cellular material for HPV can only be tested within a 3-week window, because of cellular degeneration, many clinicians have ordered reflex HPV testing. In this scenario, HPV testing is automatically performed on patients with a Pap smear reading of ASCUS before the 3-week window passes.

A large federally-funded study by the National Cancer Institute, the ALTS trial or ASCUS/LSIL Triage Study, examined the efficacy of performing reflex HPV testing on the residual cellular material remaining in the collection vial after performing a liquid-based Pap smear. In this study, women with a Pap smear diagnosis of either a

low grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASCUS) were randomized into one of three arms. The first was immediate colposcopy, the second follow-up with repeat Pap smears at a closer time interval and the third reflex HPV testing for high risk types of HPV. Reflex HPV testing was both clinically valid and cost-effective. Moreover, it is now considered the preferred method for following women who had a liquid based Pap smear diagnosis of ASCUS. In part, reflex HPV testing is preferred because it allows for further testing without the need to bring the patient back in for repeat testing. It has now become part of established evidence-based practice promoted by the **ASCCP (American Society of Colposcopy and Cervical Pathology)** to include reflex HPV testing in their practice algorithms for patients with abnormalities discovered on Pap smear.⁹

In the United States more than 50 million Pap smears are performed each year; 7%, or 3.5 million, are diagnosed as abnormal requiring further assessment or treatment.¹⁰ The majority of this group, diagnosed as requiring further assessment, are diagnosed in the ASCUS category; these patients would clearly benefit from HPV testing. Only a small proportion, approximately 176,000, will harbor a more severe high grade lesion. In comparison, roughly 11,000 to 13,000 women are diagnosed with invasive cervical cancer; 4,000 to 5,000 will actually die of cervical cancer in the United States per year. Reflex HPV testing has been found to be positive for high risk type HPV in roughly half of those patients diagnosed as ASCUS on Pap smear. Accordingly, only half of this group would require further testing, such as colposcopy, while the remainder could be safely reassured they are not likely of harboring a precancerous lesion and that they can return to regular Pap smear surveillance. For patients diagnosed with potentially more serious abnormalities, including the diagnostic categories of ASC-H (atypical squamous cells cannot exclude

high grade SIL), low grade SIL and high grade SIL, reflex HPV testing is not recommended; patients would be directed to immediate colposcopy.

Newer, more sensitive tests to detect lower quantities of HPV, such as *in situ* hybridization and PCR nucleic acid amplification are in use in some centers. These technologies have not undergone the volume of testing as the less sensitive and less expensive hybrid capture assay and are not FDA-approved.

AUTOMATED PAP SMEAR SCREENING DEVICES

One of the most serious problems associated with Pap smear examination is the fatigue factor related to the screening and evaluation of 100,000 to 500,000 cells per slide and the identification of rare atypical cells among predominantly normal cells. Image-directed cytology was designed to facilitate this process of finding the needle in the haystack and to decrease the fatigue factor. There are two such systems available; namely, the The Thinprep Imaging System developed by Cytoc Corporation, which was FDA-cleared in 2003, and the Focalpoint Slide Profiler developed by Tripath Corporation, which is also FDA-approved. These systems combine computer-assisted primary screening with human expertise.

THE THINPREP IMAGING SYSTEM

The ThinPrep Imaging System was developed as a computer-assisted primary Pap smear screening system for use with ThinPrep Pap slides. The Imager combines imaging technology with human interpretive expertise. The system consists of the Imaging Processor and one or more Review Scopes. The Imaging Processor acquires and processes image data from the slides and identifies cells or cell groups based on an algorithm that takes into consideration cellular features and nuclear darkness. Twenty-two fields of interest are recorded on x and y coordinates on each slide and the information is stored in

the computer database. The computer is also coordinated with the Review Scopes. After Image Processing, slides are distributed to cytotechnologists for review using the Review Scopes. The cytotechnologists review each of the 22 fields of interest and identify abnormal cells, if present. These cells are marked electronically and later with ink. Based on clinical trials, it was concluded that screening Pap smears using the Imager improved sensitivity and specificity. Recent studies showed that this method made a significant impact on workload and turnaround time parameters in the laboratory.^{11,12} Other studies have shown that statistically significant increases in the rate of abnormalities were seen when using the Imager.^{13,14} Statistically significant increases in the rate of LSIL (25%) and HSIL (43%) detection were seen with the Imager. The false negative fraction for the laboratory was reduced.

THE FOCALPOINT SLIDE PROFILER

The Focal Point slide profiler is another automated device intended for use in the initial screening of pap smears. The FocalPoint system identifies up to 25% of successfully processed slides as requiring no further review. The device can be used on both conventionally prepared and SurePath slides. The system classifies slides using a high speed video microscope, image interpretation software and morphology computers to image and analyze the complex images on a slide (Product Insert, Tripath Corporation). The slides that are classified as requiring No Further Review have the highest probability of being normal and may be archived by the lab as NIL. The remaining slides require manual re-screening by the cytotechnologists.

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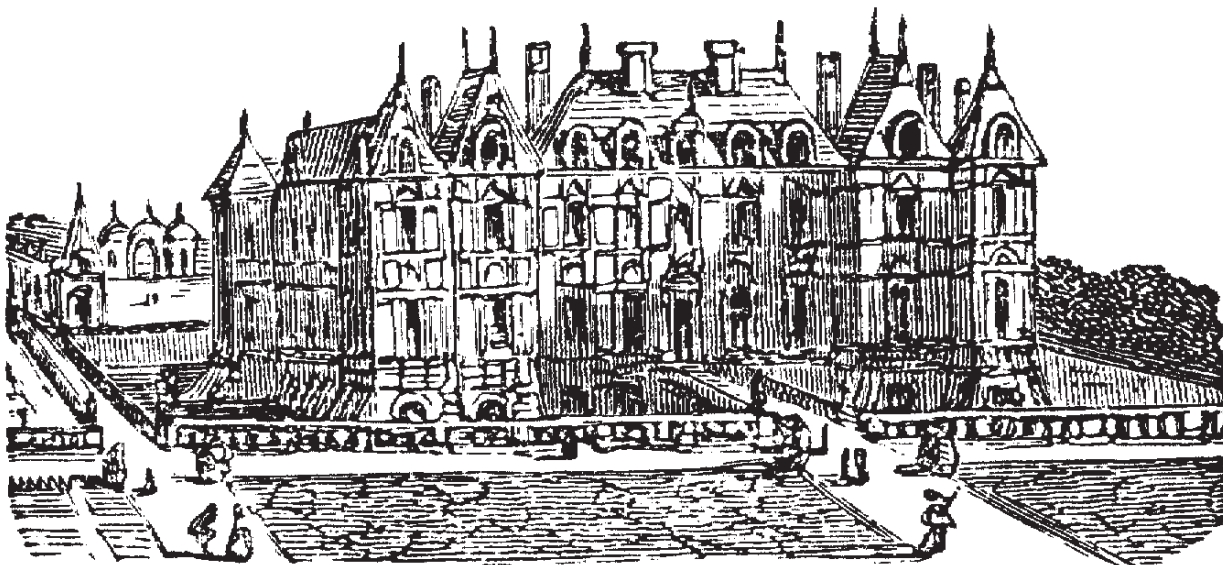
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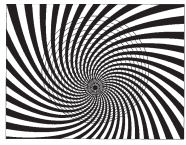
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IMAGES IN MEDICINE

PACHYMENINGITIS IN A MEXICAN IMMIGRANT

STACI A. FISCHER, MD, AND JOHN DONAHUE, MD

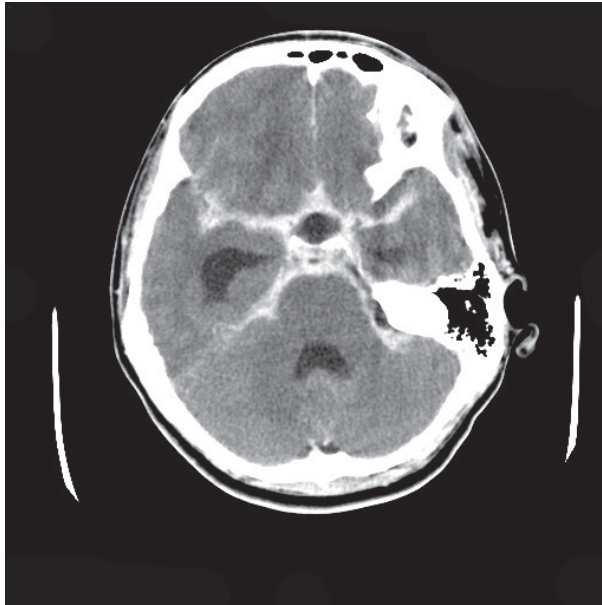


Figure 1: CT brain with contrast



Figure 2: MRI C spine

A 21-year-old male from Hidalgo, Mexico, emigrated to Virginia in June 2004. Six months later, he developed fever, night sweats and bilateral hand weakness. He was admitted to a community hospital in rural Virginia, where he was diagnosed with acute Lyme meningitis and treated with intravenous ceftriaxone; he was discharged on oral doxycycline. Four weeks later, he developed progressive upper extremity and lower extremity weakness and presented to Rhode Island Hospital with low grade fever, bilateral VIth nerve palsies, hyporeflexia in the upper extremities and bilateral upper extremity weakness. A contrast-enhanced CT of the brain (Figure 1) demonstrated hydrocephalus with prominent meninges, and MRI revealed pachymeningitis extending into the lower cervical spinal cord (Figure 2). CSF studies were noted in Table 1.

Multiple AFB cultures of CSF and PCR studies for *Mycobacterium tuberculosis* were negative. Serologic testing for *Coccidioides immitis* in blood and CSF was markedly positive, although fungal cultures of CSF were negative. A right frontal

leptomeningeal biopsy was performed, revealing chronic inflammation without granulomata. He has been treated with high doses of fluconazole and subsequently voriconazole, with slow progress noted. He is presumed to have developed coccidiomycosis while traveling to Virginia, via the southwestern United States.

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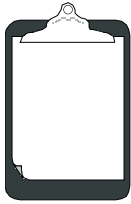
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Table 1. Cerebrospinal Fluid Studies

| Date | 1/4/05 | 2/3/05 | 2/12/05 |
|------------------|----------|----------|----------|
| Wbc's | 1075 | 162 | 3 |
| % np's/% lymphs | 43/36 | 11/83 | 1/98 |
| Protein | 601 | 6126 | 5488 |
| Glucose (serum) | 49 (N/A) | 30 (100) | 24 (137) |
| Opening pressure | 55 cm | N/A | N/A |

N/A = data not available

Possible 4/C Ad



PUBLIC HEALTH BRIEFING

RHODE ISLAND DEPARTMENT OF HEALTH • DAVID GIFFORD, MD, MPH, DIRECTOR OF HEALTH

EDITED BY JOHN P. FULTON, PHD

OSTEOPOROSIS AND YOU!

NANCY SUTTON, MS, RD, REBECCA MARTINIQUE, SHARON MARABLE, MD, MPH

THE NEED

Low bone mass (LBM) often goes undetected. It is estimated that over 50% of postmenopausal women have osteoporosis or osteopenia. Of this population, it is predicted that half have not been diagnosed and are unaware of their risk for fracture.¹ According to one survey, only 15% of women aged 45 and older who have *never* been told they have osteoporosis believe that they are at risk for the disease. In contrast to this, 64% of respondents had at least two risk factors for osteoporosis.²

remembered ever speaking to a health care provider about osteoporosis.⁶

Preventing fracture is critical to sustain the quality of life in those who suffer from osteoporosis and osteopenia. Osteoporotic fractures are often painful and life-altering. They commonly cause deformity, disability, and death. A decrease in the activities of daily living, depression, cognitive decline, and social isolation are also associated with this disease.^{4,7} Prevention needs to start with education. Women and men need: 1) To know the risk factors

with the tools needed to educate the public.

With the support of grants from pharmaceutical companies and from the Office of Minority Health of the Rhode Island Department of Health, five trainings and three recertification trainings have been offered since 2001, including 1 targeted training for professionals serving minority populations. (HEALTH also supported the translation of OY educational materials into Spanish.) A total of 103 nurses, dietitians, occupational therapists, physical therapists, and health educators were OY-certified to offer classes in senior centers, assisted living facilities, hospitals, minority health agencies, physical therapy clinics, and community centers statewide. A sixth training is planned for November 2005.

| | |
|---|---------------------------------|
| <i>Osteoporosis</i> is defined as: | LBM t-score < - 2.5 |
| <i>Osteopenia</i> is defined as: | LBM t-score < - 1.0 but > - 2.5 |

Osteoporosis is often viewed as a disease that solely affects Caucasian females. However, 20% of people with osteoporosis are men. In addition, all women, regardless of race and ethnicity, are at high risk of developing osteoporosis. Opportunities for educating African American, Asian, Native American, and Hispanic women about osteoporosis are often missed. These women frequently remain undiagnosed, and therefore miss the benefits of treatment. Although African American women typically have greater bone mass than white women, they do experience fractures. In comparison with their Caucasian counterparts, African American women who fracture are found to experience greater disability, longer hospital stays, and higher mortality.^{3,4}

It has been well documented that physicians do not routinely speak to patients about the prevention of osteoporosis and its risks. Studies find that 42-54% of respondents report that they have never spoken with a doctor about osteoporosis.^{2,4,5} In a 2003 Rhode Island survey, 63% of female respondents and only 10% of male respondents aged 50 and older

for the development of osteoporosis; 2) To speak with their doctor about their risk; and 3) To take action to maintain bone strength and prevent bone loss.

RESPONSE TO NEED

The **Arthritis Foundation (AF)**, Southern New England Chapter, the **Osteoporosis Education Program (OEP)** of the **Rhode Island Department of Health (HEALTH)**, and the **Rhode Island Osteoporosis Coalition (RIOC)** joined forces in March 2001 to offer the first **Osteoporosis and You! (OY)** instructor training. OY is an AF program that was originally designed to educate *adults with arthritis* about their risk of developing osteoporosis. However, it was also viewed as a valuable resource to educate the *general public* about osteoporosis. A 'train the instructor' model was chosen as the most efficient approach to implementation. OY consists of six modules covering 1) basic information about the development of osteoporosis; 2) diagnosis; 3) nutrition; 4) exercise; 5) fractures and fall prevention; and 6) medications. Health professionals specializing in these content areas train the OY instructors, providing them

TRAINING DESIGN

The full-day OY instructor training covers six modules on osteoporosis and one on running OY classes for the general public. Speakers at the trainings receive small honoraria (excluding those who work for state agencies or the AF). To defray training costs (including an extensive array of curriculum materials used in public education classes), a registration fee is charged, subsidized by grant funding. Fees have ranged from \$0 to \$65.

PUBLIC HEALTH APPROACH

OEP (at HEALTH, located in the Office of Women's Health, Division of Disease Prevention and Control) is a program created by the Rhode Island General Assembly in 1997. Its charge is to "use existing resources to educate the public on the causes of osteoporosis and the personal risk factors, publicize the value of early detection and prevention, and identify the most cost-effective options available for treatment."⁸

RIOC convened as the Rhode Island Osteoporosis Group in 1997. Members include representatives from agencies and organizations within the health care industry and interested individuals from the public. Members completed the *Osteoporosis State Plan, 2003-2008* in April, 2003, and became a coalition in June of that year. The Coalition is currently unfunded and receives resources from the private sector to accomplish its goals and objectives on an "as needed" basis. HEALTH provides a part-time person to staff the Coalition. It is duly noted that, unlike other life-threatening and debilitating diseases, osteoporosis is not represented by a local chapter of any national foundation or association. The RIOC members have come together to take on this charge.

AF, Southern New England Chapter, is a non-profit agency. The AF's mission is to improve lives through leadership in the prevention, control, and cure of arthritis and related diseases. Osteoporosis is a related disease because the long-term use of steroids to treat some forms of arthritis increases the risk of developing osteoporosis. The AF certifies and coordinates OY instructors. In addition to educating their own clients or patients, instructors are strongly encouraged to speak on a volunteer basis in the community year round and during Osteoporosis Awareness and Prevention Month in May.

All three agencies share the same goal: to reduce the burden of osteoporosis in Rhode Island. Each contributes to the effort through staffing, printing, educational materials, expertise in a variety of areas, and meeting space.

An example of the collaborative effort is the May 2005 public education campaign. The goal was to increase the diversity of the people we reach. Senior centers, community agencies, and worksites that reach minority populations were invited to participate. They were offered an osteoporosis screening, an information table at their health fairs, an OY presentation, and educational materials and posters.

APPLICABILITY ACROSS THE BOARD: THE MODEL

Such initiatives could not be undertaken without the brainpower, manpower, and resources that members of RIOC, OEP, and AF bring to the table. More than ever, people are educating themselves about health, advocating for themselves, and speaking to their doctors about preventing chronic disease. The public is hungry for information and resources to assist them to make lifestyle changes at a time when the economic climate does not support the staffing required to meet the demand for such requests. State agencies and health care programs must pool resources to achieve common goals.

For more information about how you can get involved with the RIOC or to learn more about the OY trainings and classes, contact Nancy Sutton at HEALTH at (401) 222-7636. The Coalition provides information to the public through the **Osteoporosis Hotline: (401) 444-6216**.

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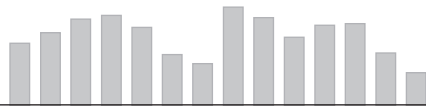
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HEALTH BY NUMBERS

RHODE ISLAND DEPARTMENT OF HEALTH • DAVID GIFFORD, MD, MPH, DIRECTOR OF HEALTH
 EDITED BY JAY S. BUECHNER, PHD

HOSPITAL INPATIENT CARE IN RHODE ISLAND, 2003: MOST COMMON DIAGNOSES AND PROCEDURES

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Patients who are treated as inpatients in the state's fourteen private acute-care hospitals are among the members of the population who are most severely impacted by illnesses and injuries. Data on these patients' care are useful for monitoring patterns of incidence and prevalence of acute and chronic health conditions in the state's population. Since 2000, the Office of Health Statistics of the Rhode Island Department of Health has summarized these data in a series of annual reports.^{1,2,3} This study presents excerpts from the most recent report, covering 2003, including data on the most commonly occurring principal diagnoses and most commonly performed procedures among hospital inpatients.⁴

METHODS

Under licensure regulations, all acute-care hospitals in Rhode Island report to the Department of Health, Office of Health Statistics, a defined set of data items on each inpatient discharge. Acute-care general hospitals have been reporting since October 1, 1989; as of October 1, 1998, two psychiatric

specialty hospitals and the inpatient rehabilitation facility began reporting. The analysis included discharges from January 1, 2003 through December 31, 2003, and employed data on the patient's sex, principal diagnosis, and procedures (up to 10 per discharge). Diagnoses and procedures are coded in the **International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)**, and were grouped as for published national data.⁵ Population-based rates for principal diagnosis groups were computed using 2000 Census data for the state and were adjusted for care provided to Rhode Island residents in Massachusetts hospitals. Comparative rates for the US for 2003 were provided by the National Center for Health Statistics.⁵

RESULTS

The fourteen hospitals reported a total of 126,784 discharges with 689,249 days of care in 2003, for an average length of stay of 5.4 days. The discharge rate per 10,000 population was 1,144.9, slightly lower (4.6%) than the discharge rate for the nation,

1,199.7 per 10,000 population). (Table 1)

The most common principal diagnosis group among hospital discharges in Rhode Island was heart disease, as was true for the nation, followed by deliveries. (Table 1) For both, the state's rates were lower than the corresponding national rates (7.6% and 14.0%, respectively). Rhode Islanders experienced higher discharge rates than the nation for the next two most common diagnosis groups, psychoses (55.1% higher) and malignant neoplasms (8.9% higher). Among the six next-ranking diagnosis groups, discharge rates for the state were higher than for the nation in two (major depressive disorder, 59.4% higher, and chronic bronchitis, 24.7% higher). For pneumonia, fractures, and cerebrovascular disease, the state's rates were lower than the nation's, by 9.1%, 12.7%, and 12.0%, respectively. The state and national discharge rates for complications of surgical and medical care were similar.

Among all discharges from Rhode Island hospitals in 2003, 60.8%

Table 1.
Hospital Inpatient Discharges with Most Common First-Listed Diagnoses,
per 10,000 Population, Rhode Island and United States, 2003

| First-Listed Diagnosis | Rate per 10,000 population | |
|--|----------------------------|---------------|
| | Rhode Island | United States |
| All conditions | 1,144.9 | 1,199.7 |
| Heart disease | 141.9 | 153.5 |
| Deliveries | 119.5 | 138.9 |
| Psychoses | 85.0 | 54.8 |
| Malignant neoplasms | 47.7 | 43.8 |
| Pneumonia | 43.7 | 48.1 |
| Fractures, all sites | 31.7 | 36.3 |
| Complications of surgical and medical care | 31.3 | 30.2 |
| Cerebrovascular disease | 29.3 | 33.3 |
| Major depressive disorder | 27.9 | 17.5 |
| Chronic bronchitis | 22.7 | 18.2 |

underwent one or more surgical or major diagnostic procedures. The most commonly performed procedures were those in the group arteriography and angiocardiology. (Table 2) More than twice as many of these procedures were performed than the next-ranking procedure, repair of obstetric laceration. Three other heart procedures, cardiac catheterization, balloon angioplasty, and insertion of coronary artery stents, were among the ten most common procedures performed.

Procedure patterns were different for males and females. For females, three of the ten most commonly performed procedures were related to childbirth, including repair of obstetric laceration, cesarean section, and medical induction of labor. For males, five of the ten most common procedures were procedures on the heart. In addition to the four appearing in the overall ranking, coronary artery bypass grafts were common procedures among males.

DISCUSSION

The patterns of utilization of inpatient care in Rhode Island during 2003, as exhibited in the data on diagnoses and procedures, reflect the

major health conditions affecting the state's population: heart disease, cancer, stroke, pneumonia, injury, mental illness, and childbirth. Among the most commonly reported principal diagnosis groups, there are two where Rhode Island's discharge rates are substantially higher than national rates – psychoses and major depressive disorders. A more detailed analysis of discharges with diagnoses of mental illness and substance abuse is in progress.

Because of the breadth of information contained in the patient-level data on hospital inpatients that are submitted to the Department of Health, these data have been widely used to investigate issues and patterns in the state's health care system. Hospital inpatients reflect the major health conditions in the state's population, so the data also have potential value in the area of public health surveillance and evaluation. By summarizing these data in a consistent format, the Department of Health's annual reports on the hospital discharge database are a key step in the development of the public health uses of these data.

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Table 2.
Most Commonly Performed Procedures,
Hospital Inpatients, by Gender, Rhode Island, 2003

| Procedure Rank | All Patients | Females | Males |
|----------------|---|---|---|
| 1 | Arteriography and angiocardiology (11,678) | Repair of obstetric laceration (5,755) | Arteriography and angiocardiology (7,041) |
| 2 | Repair of obstetric laceration (5,755) | Arteriography and angiocardiology (4,637) | Cardiac catheterization (3,036) |
| 3 | Cardiac catheterization (4,919) | Cesarean section (3,728) | Respiratory therapy (2,411) |
| 4 | Diagnostic ultrasound (4,895) | Diagnostic ultrasound (2,644) | Diagnostic ultrasound (2,251) |
| 5 | Endoscopy of small intestine (4,724) | Endoscopy of small intestine (2,590) | Endoscopy of small intestine (2,134) |
| 6 | Respiratory therapy (4,652) | Respiratory therapy (2,240) | Balloon angioplasty (1,810) |
| 7 | Cesarean section (3,728) | Hysterectomy (1,994) | Insertion of coronary artery stent(s) (1,713) |
| 8 | Endoscopy of large intestine (2,761) | Cardiac catheterization (1,883) | Coronary artery bypass graft (1,439) |
| 9 | Balloon angioplasty (2,694) | Medical induction of labor (1,857) | Hemodialysis (1,337) |
| 10 | Insertion of coronary artery stent(s) (2,561) | Endoscopy of large intestine (1,655) | Endoscopy of large intestine (1,106) |

Some names of procedure groups have been shortened; full names are: Arteriography and angiocardiology using contrast material, Repair of current obstetric laceration, Endoscopy of small intestine with or without biopsy, Endoscopy of large intestine with or without biopsy, Balloon angioplasty of coronary artery or coronary atherectomy.

PATIENT SAFETY AND CULTURE CHANGE IN HOSPITALS

LYNN MCNICOLL, MD, FRCPC, PHYLLIS J. MCBRIDE, MS, RN, AND
CATHY E. DUQUETTE, PHD, RN

NEED FOR CULTURE CHANGE

In today's healthcare environment, the term culture change is frequently referred to in conjunction with patient safety. Culture change in this context refers to changing the way healthcare providers think and act to keep the focus on the patient and to prevent harm. Over the past few years, national organizations have examined and reported on the safety of hospitals and the healthcare environment. The widespread report, "To Err is Human"¹, published by the Institute of Medicine in 1999, sparked a flurry of national and local activities to examine the relationship between the culture of an organization and its impact on patient safety. In the five years since the release of this report, the pace of change has been slow but all hospitals have implemented one or more new practices to improve safety². Quality Improvement Organizations working in partnership with the **Centers for Medicare and Medicaid Services (CMS)**, the **Institute for Healthcare Improvement (IHI)**, the **Joint Commission of Accredited Healthcare Organizations (JCAHO)**, the Leapfrog Group, the **National Quality Forum (NQF)** and others are helping to keep the focus on patient safety through various requirements and voluntary initiatives. For more detailed information on specific initiatives for each organization, refer to the Table for a list of websites.

Quality Partners of Rhode Island and other **Quality Improvement Organizations (QIOs)** across the nation work under contract with CMS to bridge the quality gap—the difference between what medical experts say should be standard practice and the care provided to Americans. Quality Partners has had significant success helping Rhode Island providers adopt best practices in hospitals, doctors' offices, nursing homes and home health services. In July 2002, JCAHO approved the first set of 6 National Patient Safety Goals with 11 related requirements for improving the safety of patient care across the healthcare environment. These goals are ways to test and implement change to existing processes in order to realize improvement in patient safety. The IHI was founded in 1991 with the mission of driving improvement in health by advancing the quality of healthcare. In December 2004, the IHI launched the 100,000 Lives Campaign with the goal of saving 100,000 lives by June 2006 by encouraging hospitals to implement changes in care that prevent avoidable deaths. The 100,000 Lives Campaign has enlisted over 2,000 hospitals across the country, including several hospitals in Rhode Island. These hospitals have agreed to focus on one or more of the following: deploy Rapid Response Teams; deliver reliable, evidence-based care for acute myocardial infarction; prevent adverse drug events; prevent central line infections; prevent surgical site infections; and prevent ventilator-associated

pneumonia.

The Leapfrog Group for Patient Safety was launched in 2000 with an initial goal of reducing preventable medical mistakes. The Leapfrog Group endorses key quality practices: computer physician order entry; evidence-based hospital referral; intensive care unit staffing by physicians experienced in critical care medicine; and The Leapfrog Safe Practices score, based on the NQF-endorsed Safe Practices. The NQF was formed in 1999 to develop and implement a national strategy for healthcare quality measurement and reporting. In 2003, the NQF released a report entitled "Safe Practices for Better Healthcare" which outlines 30 safe practices that should be applied across all clinical care settings to reduce harm to patients.

Hospitals in Rhode Island and other healthcare organizations are responding to these national efforts by working to make changes in the way that healthcare providers view what they do everyday. More and more, hospital and quality improvement leaders are examining the way care is delivered with a renewed and specific focus on patient safety. In a culture of safety, health care providers are encouraged to take action when it is needed to prevent patient harm. The only way that a culture of safety can truly exist is when organizational leaders are actively committed to change and employees are willing to report unsafe conditions without fear of retribution. The IHI has identified a number of changes that will drive an organization towards a culture of safety which include: providing feedback to front-line staff; conducting patient safety leadership WalkRounds[™]; conducting safety briefings; relaying safety reports at shift changes; and appointing a safety champion for every unit.

BENEFITS OF CULTURE CHANGE

Patients are not the only ones who benefit from culture change. Healthcare providers also become educated and empowered to effect positive change and this is especially important for nurses. This empowerment results in a tremendous sense of fulfillment and self-worth in employment and the profession. Many nurses and healthcare providers feel that they have lost the sense of commitment and dedication to the principles of healthcare that led them to this field in the first place. Once they become involved in a culture change initiative, there is a return to the core reason for being in healthcare – to improve the health and well-being of patients. Early feedback from hospital staff participating in a statewide ICU collaborative in Michigan led by the Michigan Hospital Association and called "MHA Keystone: ICU Project" has been very positive. Some participants report that newer nurses feel more comfortable and are made to feel like part of the team. Others identify that the patient has become the main focus again.³

Effective benefits become improvement in staff satisfaction and subsequently, staff retention. Disenfranchised staff members suddenly become vibrant and active members of the team. Disturbing rumblings about dissatisfaction turn to public commitment and praise. Staff members have a renewed sense of pride in their work, thus leading to a perpetual push for improvements regardless of past achievements. This positive and infectious environment is readily noticeable by others, including patients and families. Patient and family satisfaction is likely to improve with this attitudinal change.

In addition, clinical outcomes are expected to improve. Culture change is usually combined with an evidence-based, targeted program to improve care for hospitalized persons. Culture change is one of the strategies for initiation, implementation and sustainability of these evidence-based strategies. Again how do we know this? In today's healthcare environment, efficiency is vital to a successful healthcare delivery. Often, however, efficiency leads to practices that are not patient-focused but rather practitioner-focused. A component of culture change is recognizing which practitioner-focused practices have the potential to indirectly harm patients and could be altered without radical changes in efficiency. Many culture change programs work on reorganization of the working structure of the units, actually improving the efficiency of the unit as a whole. With improvement in patient safety, complications and iatrogenic events are reduced. This leads to shorter lengths of stay, reduced morbidity and, perhaps, reduced mortality.

With better clinical outcomes, improved satisfaction and improved efficiency, cost savings are often obtainable. Generally, culture change strategies are not meant to reduce costs, and may actually be costly to implement. Patient safety and culture change initiatives require expert advice and project management. Healthcare providers also need to get some education about the project and continued reinforcement. Monitoring of processes and outcomes also require funds. However, improved patient outcomes result in cost savings for the hospital, reduced legal action, improved contribution margin and cost avoidance.

KEYS TO SUCCESSFUL CULTURE CHANGE

Barriers to culture change with respect to clinical programs and patient safety are many and daunting. However, there are key strategies that have been shown to increase the likelihood of success. Culture change initiatives must include administrative support and endorsement. Most

culture change programs require some financial support, which needs to be provided by the administration up-front and sustained for the duration of the program. In addition to financial support, it is important for staff members to understand that the executive branch considers the program a priority and is aligned with the mission and strategic plan for the institution.

It is crucial to include all members of the team in the implementation and development of a project from the initial stages. This will ensure buy-in from staff rather than having the staff feel that the project is an imposition. Nursing staff and other healthcare professionals working in the hospitals are burdened with increasing demands. Culture change strategies can help providers move beyond initial reactions of anxiety and rejection to one of embracing the underlying principles and benefits of the program. Transferring the focus of patient safety away from an individual error or blame to that of a system issue as was clearly articulated in the "To Err is Human" report has helped in the buy-in of patient safety initiatives. This has formed the fundamental foundation for moving patient safety forward and has shifted the focus away from individuals to systems.

Education about the evidence-based nature of the project is crucial for healthcare providers to embrace and understand the principles behind the project. Demonstrating success of the project in other institutions or units can be a quite powerful motivator. If Unit A did so well and now has better outcomes, why can't our unit have the program? Testimonials from units or hospitals that have been successful and benefited from the program can improve buy-in and compliance with the program in other sectors of the hospital.

CULTURE CHANGE PROJECTS IN RHODE ISLAND

Rhode Island is a leader in patient safety and quality improvement initiatives. Hospitals in Rhode Island, as a group, ranked first among all states on the first publicly reported quality indicators as reported on the Hospital Compare website released in April 2005. The State continues to pursue quality and patient safety through involvement in the IHI 100,000 lives campaign and through the following examples.

The Intensive Care Unit (ICU) Collaborative. Quality Partners of Rhode Island and the Hospital Association of Rhode Island, in partnership with the Rhode Island Quality Institute of Rhode Island, are exploring the opportunity to launch a statewide project, the ICU Collaborative, with

Table 1.

| ORGANIZATION | WEBSITE |
|---|--|
| Centers for Medicare and Medicaid Services | www.cms.hhs.gov |
| Institute for Healthcare Improvement | www.ihl.org |
| Joint Commission on Accreditation of Healthcare Organizations | www.jcaho.org |
| Leapfrog Group | www.leapfroggroup.org |
| National Quality Forum | www.qualityforum.org |

consultation from national leaders in ICU care improvement, to dramatically improve ICU care in Rhode Island. This ICU Collaborative aims to rapidly adopt the successful changes already yielding dramatic improvements in ICUs across the country. Three states - Michigan, Maryland, and New Jersey - have already embarked on statewide ICU collaborative improvement efforts. These states are now working together to share best practices and other materials to facilitate improvement efforts and minimize duplication of effort.

The Miriam Hospital GENESIS Project. The Miriam Hospital initiated the GENESIS project in 2002 to improve the care of older persons admitted to the hospital, where 60% of The Miriam patient population is aged 65 and over. The project involved three days of education for nurses and aides, strategic environmental changes and implementation of validated, evidence-based geriatric protocols (mobility, nutrition and sleep) to prevent complications of hospitalization such as delirium, falls, pressure ulcers, deconditioning and the morbidity associated with these negative outcomes. The GENESIS project has been tremendously successful in large part due to the culture change that occurred towards the care of older adults and the organizational change that occurred at the unit level. More information about GENESIS will be presented in detail in a September article in The Rhode Island Medical Society Journal.

CONCLUSION

Patient safety initiatives and culture change are integral to improving the care of hospitalized patients and are not mutually exclusive. Rhode Island is a leader in this field; in the coming editions of Rhode Island Medical Society Journal, we will further examine two projects where RI is improving the care of hospitalized persons – the statewide ICU Collaborative and the Miriam Hospital GENESIS project.

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A PHYSICIAN'S LEXICON

DRAWING THE BREATH OF LIFE

The respiratory system has accumulated an abundance of medically oriented words to describe its various anatomic elements.

The Greek word for lung, *pneuma*, originally defined an intangible substance, a gas perhaps, which imparted the essence of life to the body. Hence, *pneuma*, also described the fundamental essence, the inner spirit of the body. This earlier meaning persists in the word, pneumatology, the study of spiritual values. The word was adopted by Roman physicians, some of whom formed a sect called the pneumatists, believing that health and disease were determined by the airborne spirits within the body. The spiritual component of breathing is seen in such words as respiration, from the Latin, *respirare*, which is etymologically related to the Latin, *spiritus*, the breath of life. A variety of current words stem from this Greek root, *pneuma*, including pneumatic, pneumococcus, pneumoconiosis and

pneumonia.

The Latin equivalent of *pneuma* is *pulmo-*, a root which also means to swim or float. In Roman abattoirs, the animal organs were routinely rinsed in water and since the lungs were the sole organs which floated, the word conveyed the parallel meaning of lightness. Indeed, until the 18th Century, the vernacular word for lungs, in England, was "the lights."

Pleura was a Greek word meaning rib or the side of the animal. Mondino, the great anatomist, first used the word to describe the membrane enveloping the lungs. Pleurisy [or rarely, pleuritis] describes inflammatory disease of the pleura. But pleurodynia, pain in the chest, harkens back to the earlier meaning of pleura, namely, pertaining to the entire chest wall. The word, plural, however, is derived from the Latin, *pluris*, meaning more than one.

Bronchus, a Greek word currently meaning a windpipe but originally

meaning a passage for the pouring of liquids, derives from the ancient belief that solid foods were conveyed to the stomach via the esophagus and liquids via the bronchi. The word, *trachea*, is a Greek word meaning rough. And since Greek anatomists believed that the trachea was a rough artery, it was then called *arteria trachea*. By the 15th Century, the adjectival *arteria* was dropped.

Alveus, a Latin word meaning trough or hollow, was used by Vesalius to describe the socket of a tooth; and then later by Malpighi when he was seeking a better word for the terminal air spaces in the lungs. He then added a diminutive suffix thus coining the word, *alveolus*. The prefix, *al-*, as in *alveus*, is solely Latin. Many scientific words beginning with *al-*, however, are of Arabic origin such as alkali, alchemy, alizarin, algebra and alcohol.

-STANLEY M. ARONSON, MD



RHODE ISLAND DEPARTMENT OF HEALTH
DAVID GIFFORD, MD, MPH,
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VITAL STATISTICS

EDITED BY ROBERTA A. CHEVOYA, STATE REGISTRAR

Rhode Island Monthly
Vital Statistics Report
Provisional Occurrence Data
from the
Division of Vital Records

| Underlying Cause of Death | Reporting Period | | | |
|--------------------------------------|------------------|---------------------------------|-----------|----------|
| | July 2004 | 12 Months Ending with July 2004 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 238 | 3,047 | 284.8 | 5,091.0 |
| Malignant Neoplasms | 223 | 2,495 | 233.2 | 7,653.5 |
| Cerebrovascular Diseases | 34 | 512 | 47.9 | 765.0 |
| Injuries (Accident/Suicide/Homicide) | 42 | 458 | 42.8 | 7,069.0 |
| COPD | 25 | 482 | 45.1 | 475.0 |

| Vital Events | Reporting Period | | |
|--------------------------|------------------|------------------------------------|--------|
| | January 2005 | 12 Months Ending with January 2005 | |
| | Number | Number | Rates |
| Live Births | 933 | 13440 | 12.6* |
| Deaths | 1076 | 9974 | 9.3* |
| Infant Deaths | (4) | (63) | 4.7# |
| Neonatal deaths | (4) | (53) | 3.9# |
| Marriages | 304 | 8241 | 7.7* |
| Divorces | 255 | 3,245 | 3.0* |
| Induced Terminations | 451 | 5,472 | 407.1# |
| Spontaneous Fetal Deaths | 24 | 978 | 72.8# |
| Under 20 weeks gestation | (18) | (903) | 67.2# |
| 20+ weeks gestation | (6) | (75) | 5.6# |

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,069,725

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population

Rates per 1,000 live births

NINETY YEARS AGO, JULY 1915

An Editorial summarized the ruling by The Commission of Internal Revenue on the Harrison Law. "Physicians who prescribe an unusual quantity of either opium or cocaine in a quantity more than is apparently necessary to meet the immediate needs of a patient in the ordinary case, or where it is for the treatment of an addict or habitué to effect a cure, or for a patient suffering from an incurable or chronic disease, such physician should indicate on the prescription the purpose for which the unusual quantity is to be used. In cases of treatment of addicts, these prescriptions should show the good faith of the physician in the legitimate practice of his profession by a decreasing dosage of the quantity prescribed from time to time, while on the other hand in cases of chronic or incurable diseases, such prescriptions might show an ascending dosage or increased quantity."

Stephen Welch, in President's Annual Address: Some of the Conditions Affecting the Practice of Medicine in the City of Providence," gave statistics. In 1874 the city had 1 physician for every 4696 people; in 1884, the ratio rose to 1:523; in 1904, 1:536; by 1914, 1:591. When he included midwives, osteopaths, and Christian Science practitioners in his calculations (Dr. Welch: "There are a number of individuals in Providence of whom it has been said that they entered the Temple of Medicine by a rear window"), the ratio was 1:553. In 1865, 5 physicians worked in hospitals; by 1914, 185 (50% of physicians) did. Dr. Welch reminded readers that hospital work was "usually without pecuniary reward." Specialists too had grown in number. In 1865 only 1 physician in 40 was a specialist; by 1913, 1 in 6 specialized. Before 1904, the City of Providence employed 3 physicians; in 1914, the City employed 18. Residents too were seeking out hospital stays: from 1864 to 1874, 1 resident in 47 went to a hospital; from 1904 to 1914, 1 in 10 had stayed in a hospital.

Frederic V. Hussey, MD, in "Acute Intussusception in Infants," described 4 infants whom he had operated on at Memorial: 2 died.

FIFTY YEARS AGO, JULY 1955

Somers H. Sturgis, MD, Associate Clinical Professor of Gynecology, Harvard Medical School, in "The Use and Abuse of Hormones," discussed the benefits of a range of hormones: e.g., thyroid, adrenal, pituitary, ovarian, progesterone, testicular.

Charles L. Farrell, MD, in "A Re-Appraisal of Medico-Economic Problems," urged the state Medical Society's "studying committees" to focus on voluntary health insurance, social security, re-insurance, temporary disability compensation, worker's compensation, malpractice, and fee-splitting.

Harold W. Harrower, MD, and Philip Cooper, MD, contributed "Obstructive Jaundice due to Chlorpromazine,"

a case report from the Veterans Administration Hospital.

An Editorial, "Cancer Chemotherapy," gave cautious support to the recently-established Cancer Chemotherapy National Committee, chaired by Dr. Sidney Farber of Children's Center in Boston. "Probably a good many of us would be skeptical about the cancer problem being solved by the use of drugs, but what does our skepticism amount to here? Practically nothing is known definitively about the cure of cancer. Every lead must be followed up...."

TWENTY-FIVE YEARS AGO, JULY 1980

The Journal printed the papers submitted to a Symposium on the Immediate Care of the Traumatized Patients: Arnold Herman, MD, FACS, "Immediate Evaluation of the Multiply Injured Patient;" William E. Kaye, MD, "Advanced Cardiac Life Support;" Herbert B. Hechtman, MD, Arnaldo M. Vegas, MD, and Gene A. Grindlinger, MD, "Diagnosis and Treatment of Respiratory Failure;" Louis Vito, Jr., MD, "An Evaluation of Intra-Abdominal Injuries;" M. Terry McEnany, MD, "Emergency Care of Chest Injuries;" Harold J. Levinson, MD, "Management of Peripheral Arterial Trauma;" Howard S. Sturim, MD, "Evaluation and Treatment of the Injured Hand;" Stephan D. Deutsch, MD, "Evaluation and Immediate Care of the Patient with Spinal Trauma;" and Albert E. Carlotti, Jr, DDS, "Acute Care of Facial Injuries and Reconstructive Opportunities."

In "Dean's Message: The State of Rhode Island Internships, 1980-81," Stanley M. Aronson, MD, reported on the 103 interns: most matched via the National and Resident Matching Program; 32% were women (up from 21% in 1979-80).

Alan M. Deutsch, MD, Michael J. Ryvicker, MD, Howard Cohen, MD, and Sanford Schatz, MD, contributed "Radiographic Case of the Month," with views of the left hip and the thoracic spine in a 20 year-old man who presented with intermittent episodes of abdominal and extremity pain. The diagnosis was sickle cell anemia.

FORTHCOMING

Medicine & Health/Rhode Island

August 2005

Medical Education

Guest Editor:

Stephen R. Smith, MD, MPH

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