lished baseline error proportions in both gynecologic and nongynecologic cytopathologic services and measured the effect of discrepancies and errors on patient outcomes by performing medical record review.

RESULTS: Institutional discrepancy frequencies varied from 2–12% of all cytopathologic specimens, and up to 40% of errors resulted in patient harm, often consisting of repeat testing or delays in diagnosis. The major cause of error was poor specimen quality, and a percentage of poor-quality cancer specimens were interpreted as normal by cytopathologists. Real-time observations showed that up to 35% of specimens were “faulty” and a setup for medical error. Institutional preanalytic and analytic practices were unstandardized, and the lack of standardization contributed to differences in discrepancy proportions.

CONCLUSION: Diagnostic testing errors most often result in mild or minimal harm from overtesting or diagnostic delays. Improvement in patient safety could result from increased sharing of error data and redesigning testing systems by standardizing preanalytic and analytic processes.

From University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A.

IL-34 AFRICA CALLS: A TEACHING TELECONFERENCE WITH 18 UNIVERSITIES IN AFRICA

David Kaminsky—Why and How Malcolm Hayes—Cytopathology of Breast—Some interesting cases Bryan Knight—Closing comments

From Palm Springs Pathology Services, Palm Springs, California, U.S.A., and Department of Pathology and Laboratory Medicine, British Columbia Cancer Agency, Vancouver, British Columbia, Canada.

CYOTECNOLOGISTS’ MEETING: PANEL CYTOTECHNOLOGISTS WORKING IN RESOURCE-POOR SETTINGS

CY-01 MOLECULAR DIAGNOSTICS FOR CYTOPATHOLOGY

E. Blair Holladay

Abstract not available at the time of going to press.

From American Society for Clinical Pathology, Chicago, Illinois, U.S.A.

CY-02 INTRODUCTIONS AND OVERVIEW

Theresa M. Somrak

Abstract not available at the time of going to press.

From American Society for Clinical Pathology, Chicago, Illinois, U.S.A.

CY-03 KENYA AND THE PAPS PROGRAM

Mark Titus

Abstract not available at the time of going to press.

From Loma Linda Hospital, Loma Linda, California, U.S.A.

CY-04 NATIVE AMERICAN SEE AND TREAT PROJECTS

K. Allen

There are no cytotechnologists, pathologists or gynecologists on the Standing Rock or Rosebud Indian Reservations in South Dakota. When a woman has a Pap test collected by the local general practitioner or nurse midwife, it is sent far away to a laboratory for processing. If follow-up surgical treatment is necessary, the Native American patients must travel approximately 100 miles for treatment. The purpose of the See and Treat project is to provide an opportunity to underserved populations to receive medical screening examinations with immediate follow-up treatment. Because cancer survival rates are directly related to the stage of the disease at the time of diagnosis, it is important to remove all barriers to early diagnosis and treatment. Women who rarely, if at all, get Pap tests are at higher risk for developing and dying from cervical cancer. By keeping the patient on site while their tests are processed, any follow-up care can be provided at the same visit. This decreases the chance of losing patients to appropriate follow-up care and increases their survival.

From Heartland Pathology, U.S.A.

SATELLITE SYMPOSIA

BRITISH SOCIETY FOR CLINICAL CYTOLOGY SATELLITE MEETING: CHANGING PRACTICE AND ITS EVALUATION IN A NATIONAL CERVICAL SCREENING PROGRAMME IN THE U.K.

SS-01 INTERNAL AND EXTERNAL PRESSURES FOR CHANGING PRACTICE IN CYTOLOGY IN THE U.K.

A. Herbert

The main external pressures for cytology lie in the expense of liquid-based cytology (LBC), the potential of automation, the development of molecular markers and the probable piecemeal introduction of vaccination. Cytopathologists throughout the world face the challenge of moving toward a more varied approach to cytologic diagnosis, with less emphasis on morphology alone and a gradual decline in cervical cytology. In some ways the UK, having already introduced LBC, should be in a position to exploit its advantages such as automation and the availability of material for molecular markers. Quality control measures are stringent, which would be increasingly necessary if rates of abnormality were to decline with vaccination. However, there are internal pressures, which might make some of these challenges threats rather than opportunities. LBC
was introduced in the U.K. as a possible cost-saving measure because it reduced inadequate rates and screening times in the pilot sites. However, the costs may be higher than expected, which could jeopardize the development of the techniques that LBC makes possible and compromise its true potential. Furthermore, nongynecologic cytology has long suffered in the U.K. from workload pressures of cervical screening. LBC and the Advanced Practitioner grade have both taken some pressure off consultants, but nongynecologic cytology could be further eroded if cost-savings in cervical cytology were not achieved and if automation and vaccination were simply viewed as further cost-saving opportunities. Biomedical scientists in the U.K. are trained in general laboratory science and should be well placed to expand into new areas such as molecular diagnostics, as well as playing a greater role in developing cost-effective techniques such as fine needle aspiration cytology. The main challenge is to encourage managers to take a broader view of the costs of cytology tests so that these techniques can be expanded as workload in cervical cytology declines.

From Guy’s and St. Thomas Hospitals, National Health Science Foundation Trust, U.K.

SS-02 CHANGING ROLES OF BIOMEDICAL SCIENTISTS AND CYTOTECHNOLOGISTS

N. Dudding

As you are already aware, gynecologic cytology as we know it is coming under increasing pressure. The U.K. has already seen the national introduction of liquid-based cytology (LBC), and it is increasingly likely that we will see the introduction of automated screening, human papillomavirus testing, molecular markers and, of course, vaccination. My colleagues in this BSCC Symposium will expand on such issues, and I will restrict my presentation to the changing roles, both recently and in the future, of the Biomedical Scientist (BMS) in the U.K. BMS staff are graduates who have many roles, which can include reporting both gynecologic and nongynecologic samples. More recently, however, we have seen the introduction of a Consultant equivalent grades—the Advanced Biomedical Scientist Practitioner. These individuals are able to report on all types of gynecologic cytology and advise on patient management. This grade has proved to be very successful, and I will outline our experiences in the development and everyday practice of this grade. Beyond this, I will discuss where I think the future lies, especially with regards to bringing any new tests into histopathology or cytology laboratories rather than other units and extending our roles into previously unknown areas. In the U.K., BMSs are becoming increasingly involved in specimen dissection, reporting unfavorable biopsies and those biopsies taken as a result of the bowel screening program. With the correct training and examination program, why shouldn’t we also be allowed to report basic histopathology in other areas? This could be cervical loop electrosurgical excision procedure (LEEP) biopsies, but why not the appendix or vas deferens? The role of the BMS in nongynecologic cytology is also being developed. Although behind many other areas in the world, BMS staff are increasingly involved in reporting such samples. I will present some arguments for and against all of these possibilities.

From East Pennine Cytology Training Centre, Leeds, U.K.

SS-03 IMPLEMENTATION OF NEW TECHNOLOGIES IN THE U.K.

M. Desai

The U.K. is proud of its well-organized cervical screening program. The role of the National Health Service Cervical Screening Programme in reducing mortality from cervical cancer and improving survival rates are acknowledged in a new report published by the Office for National Statistics (October 2005). Since its introduction in 1988, it is estimated that the call and re-call program prevented 1,100–3,900 cases of invasive cancer in the U.K. each year. However, the program is constantly looking into methods of improving the uptake, performance in the laboratories and histopathology standards. Quality assurance (QA) is a fundamental part of the program. Since 2003, there are several independent trials funded by either the Department of Health or U.K. Health Technology Assessment (HTA), looking into the introduction of new technologies in cervical screening in England. The evidence gathered by these trials is presented to the National Institute for Health and Clinical Excellence (NICE), who make the final recommendation of the implementation of new technology (or not, as the case may be) in England. The introduction of liquid-based cytology (LBC) began in October 2003 following a recommendation by NICE, and half of all cytology laboratories in England have now fully implemented or started implementation of LBC. Human papillomavirus (HPV) triage for borderline and mild dyskaryosis smear result is planned to start at selected sentinel sites in early 2007. The value of the HPV test as a primary screening tool in the U.K. is being assessed by a large HTA-funded randomized trial (ARTISTIC Trial). The result of this trial is expected in early 2007. Automation in cytology laboratories is also being assessed by a large randomized HTA-funded trial (MAVARIC trial) and the results are expected in 2008. Other technologies such as new LBC machines, immunology markers and cervical cancer vaccines are at different stages of evaluation. A comprehensive summary of these various trials looking into introducing the new technologies in cervical screening in the U.K. will be presented.

From Manchester Cytology Centre, Manchester Royal Infirmary, U.K.

SS-04 EVALUATION OF THE U.K. SCREENING PROGRAM AND EMERGING ISSUES

J. Smith

Following the reorganization of the National Health Service Cervical Screening Programme (NHSCSP) in 1988, incorporating a comprehensive system of call and re-call, training and quality assurance, there has been a progressive decline in incidence of and mortality from cervical cancer. Incidence has fallen by 5% year on year, and in 2003, for the first time, there were <1,000 deaths from cervical cancer in England. The NHSCSP is estimated to prevent up to 3,900 deaths per annum. Quality assurance (QA) is pivotal to periodic evaluation of the program and encompasses all stages of the screening process from invitation to treatment of identified lesions. Regional quality assurance teams assess various aspects of each stage of the screening process against national standards determined by professional consensus, and remedial action is instituted where indicated for any identified deficiencies. Cytology laboratory QA is also closely linked to laboratory accreditation. Key standards for individual laboratories are the percentage of adequate samples report-
ed as low grade (borderline or mild dyskaryosis; atypical squamous cell [ASC], atypical glandular cells of undetermined significance [AGUS] or low-grade squamous intraepithelial lesion [LSIL]) and high-grade (moderate or severe dyskaryosis; high-grade squamous intraepithelial lesion [HSIL]) compared with the 10th–90th percentile of the range of all laboratories and the positive predictive value of high-grade squamous abnormality for the diagnosis of CIN2 or worse. Laboratories that lie outside the range are assumed to include those that have extremes of sensitivity and specificity. However, this methodology takes no account that individual laboratories screen populations with different underlying risks of cervical neoplasia, age distribution or screening interval, and emerging methodology that corrects for these variables and permits valid comparison of laboratories will be described. In addition, the potential effect of national implementation of liquid-based cytology on laboratory performance indicators and methods for continual monitoring of laboratory staff performance will also be described.

From Royal Hallamshire Hospital, Sheffield, U.K.

EUROPEAN FEDERATION OF CYTOLOGY SOCIETIES AND EUROPEAN SOCIETY OF PATHOLOGY JOINT SATELLITE MEETING: CYTOPATHOLOGY AT THE CROSSROADS

SS-05 CYTOPATHOLOGY AT CROSSROADS: INTRODUCTION

F. Schmitt

Now and in the future, cytopathologists will play a vital role in the emerging world of molecular medicine. Although ancillary techniques have become part of the diagnostic armamentarium in the laboratory, morphologic analysis coupled with detailed clinical information still play a pivotal role for diagnosis. Moreover, morphology is essential to select the target cells for molecular approach. Nowadays, cytopathology is a specialty that should be practiced together with other related specialties. The idea of this symposium is to demonstrate the role of cytopathologists at crossroads with surgeons, radiologists and oncologists. The intraoperative touch imprint cytology of sentinel lymph nodes in patients with breast cancer; intraoperative fine needle aspiration (FNA) of abdominal masses; scrape preparations for intraoperative diagnosis of central nervous system tumors, as well as the utilization of cytology together with frozen sections, are examples of the utility of cytology in the surgery theater. Interventional radiology is another field in which cytopathology has a very important role. Ultrasound guidance is a useful adjunct of FNA in different organs, decreasing the number of inadequate specimens, increasing specificity and sensitivity and allowing in some situations the diagnosis of incidental and nonpalpable carcinomas. The advent of 1-stop diagnostic services is prompting further development of FNA clinics in which cytopathologists take their own samples, working closely with radiologists and issue reports in the same clinical session. Another important development is the increasing use of endoscopic ultrasound-guided FNA for the assessment of intraabdominal and intrathoracic tumors. The use of this approach to study c-KIT mutations in gastrointestinal stromal tumors (GISTs) was recently demonstrated by our group. Cytopathologists will be also expected to include specific prognostic and predictive information in their reports. Since the last decade, there have been an increasing number of new drugs whose indications depend on a pathologic report, as in lung cancer, breast cancer and GISTs.

From IPATIMUP and Medical Faculty of Porto University, Oporto, Portugal.

SS-06 CYTOPATHOLOGY AT THE CROSSROADS WITH SURGEONS IN THE SURGERY THEATER

I. Amendoeira

Intraoperative consultation for proper therapeutic and other decisions is a standard practice. Intraoperative cytology (IC) alone or as an adjunct of frozen section (FS) is crucial but must be performed by experienced pathologists. Most intraoperative diagnosis can be accurately performed with cytology only, saving time and money because it is much quicker than FS and less sophisticated. For an effective IC consultation, facilities should be available not only for collection, preparation and staining for immediate diagnosis, but also for collection for additional studies. IC can also be used for training as a part of continued learning process. It is also an excellent opportunity for generating an archival library of rarely observed lesions. IC is particularly useful in cases of very small specimens, bone lesions, lesions difficult to access by surgical section, specimens that need several samples, and necrotic material. Procedures must be followed so that quality is ensured. The technique for slide preparation depends on the tissue to be analyzed, with direct preparation, scrape smears, crush and touch smear being the most common. Interpretation of the smears must take into account the high cellularity, presence of tissue fragments and better cellular preservation (larger nuclei with coarse chromatin and prominent nucleoli). Reporting must be clear, but a definite diagnosis should be avoided. Final judgment must take into consideration the clinical history, complementary tests and surgeon report. Whenever in doubt, a frozen section must be considered. The most commonly reported organs for IC and diagnostic accuracy rates are brain, 93.3–97.3%; lymph node for metastatic tumors, 99–99.2%; breast, 95%–99%; pancreas, 90–100%. In our experience IC is usually used alone, for breast (sentinel lymph node and margins with an accuracy of 93% and 100%, respectively) and pancreas (FNA: PPV 98%, NPV 95%).

From IPATIMUP, Hospital São João, Oporto, Portugal.

SS-07 CYTOPATHOLOGY AT A CROSSROADS WITH RADIOLOGY ON INTERVENTIONAL IMAGING: OPTIMIZING RESULTS FROM FINE-NEEDLE ASPIRATION OF THE BREAST

N. Sniege

Fine needle aspiration (FNA) of the breast is used extensively in many medical centers, primarily for the first-line assessment of nonpalpable breast lesions. Compared with core needle biopsy, FNA is favored by radiologists because its smaller needle makes it less invasive; in addition, for very small lesions or for those just under the skin or very close to the chest wall, FNA is easier and safer. In most cases, FNA specimens display characteristic cytologic features that allow accurate lesion categorization. However, to optimize the results from breast FNAs while avoiding false positive and false negative diagnoses, the radiologist must be provided with the lesion cat-
SS-08 CYTOPATHOLOGY AT THE CROSSROADS WITH ONCOLOGISTS ON MOLECULAR FEATURES FOR TAILORED THERAPEUTICS

L. Bubendorf

OBJECTIVE: The constantly growing number of tailored therapies in cancer requires selection of patients based on molecular features. Since cancer is often diagnosed in cytologic specimens, assessment of therapeutic targets has become both a necessity and a challenge in cytopathology.

METHODS: An array of different methods is needed to adequately determine the status of therapeutic targets. In situ investigations such as immunocytochemistry (ICC) and fluorescence in situ hybridization (FISH) allow determining protein expression and genetic alterations by microscopy of slides that were used for cytomorphologic diagnosis. Important examples include ICC for estrogen receptor expression and FISH for HER2 and TOP2A gene copy number analysis in breast cancer. In non–small cell lung and colorectal cancer, gene copy number analysis of the epidermal growth factor receptor (EGFR) gene may be valuable in selecting patients for therapy directed against EGFR. FISH analysis is greatly facilitated by automated relocation of cancer cells after hybridizations. It allows for selectively analyzing pure cancer cells that could otherwise be hidden in a background of benign cells. Other than in situ investigations on the slide, DNA extraction for subsequent polymerase chain reaction and mutation analysis requires removal of the tumor cells from the slides. This is best achieved by laser microdissection of selected tumor cells. Laser microdissection is applicable to previously stained cytologic specimens. It avoids dilution of tumor DNA with undesired DNA from normal cells. Mutation analysis works well with as few as 30 tumor cells. One of the currently most important examples in cytology is EGFR sequence analysis in lung cancer, in which mutation is a strong predictor of response to targeted therapy with EGFR inhibitors.

CONCLUSION: The molecular tools and techniques are available to meet the molecular challenges of analyzing therapeutic targets in routine cytologic specimens.

From M. D. Anderson Cancer Center, Houston, Texas, U.S.A.

SS-09 A DUO OF DIAGNOSTIC CHALLENGES IN FINE NEEDLE ASPIRATIONS OF THE THYROID: THE “SUSPICIOUS FOR FOLLICULAR NEOPLASM” AND “SUSPICIOUS FOR PAPILLARY CARCINOMA” CATEGORIES

M. Auger

OBJECTIVE: By the end of this session, the participants should be familiar with the cytomorphologic features of thyroid fine needle aspiration (FNA) samples that should be diagnosed as “suspicious for follicular neoplasm”; the cytomorphologic features of thyroid FNA samples that should be diagnosed as “suspicious for papillary carcinoma”; histopathologic follow-up of thyroid FNA samples diagnosed as “suspicious for follicular neoplasm” or as “suspicious for papillary carcinoma.” The diagnostic terminology used for thyroid FNA samples will be briefly outlined, with emphasis on the “suspicious/indeterminate” category. The cytomorphologic features of the FNA samples that should be diagnosed as “suspicious for follicular neoplasm” or as “suspicious for papillary carcinoma” will be amply illustrated, as well as their potential mimics. The breakdown of the follow-up histopathologic diagnoses in these 2 “suspicious” categories will be summarized by presentation of the data from key follow-up studies published in the literature. The clinical implications of such FNA diagnoses will be discussed briefly.

From the Department of Pathology, McGill University Health Center, McGill University, Montreal, Quebec, Canada.

SS-10 DIAGNOSTIC DILEMMAS IN FINE NEEDLE ASPIRATION OF THE HEAD AND NECK: SALIVARY GLAND

M. Weir

There has been substantial literature on the morphologic findings of liquid-based preparations (LBP) for gynecologic cytology, but limited attention to LBP for nongynecologic samples. In this overview of salivary gland fine needle aspiration biopsies (FNABs), the morphologic features of ThinPrep prepared salivary gland FNABs will be contrasted and compared to conventional smear preparations using case examples. As well, specific diagnostic pitfalls of and proposed diagnostic terminology for TP prepared salivary gland FNABs will be discussed.

From London Health Sciences Centre, London, Ontario, Canada.

SS-11 DIAGNOSIS OF HEAD AND NECK LYMPHADENOPATHY BY FINE NEEDLE ASPIRATION: OPPORTUNITY OR OXYMORON?

W. Geddie

Most nodes in the head and neck are easily aspirated, allowing samples from multiple nodes to be compared, and small nodes in inti-
mate juxtaposition with vessels and other anatomic structures to be sampled safely where core or excisional biopsy might be dangerous or impossible. Although the value of fine needle biopsy in the diagnosis of lymphadenopathy was convincingly articulated and beautifully illustrated by Pavlovsky in 1933, it is still controversial. Some histopathologists and clinicians are willing to endorse it only for triage or as a harvesting method for other tests and remain skeptical that primary cytopathologic diagnoses are ever sufficient for treatment purposes. In fine needle samples from head and neck nodes diagnostic problems can arise because of ambiguity about the actual anatomic site of a lesion, and morphologic mimery between disparate entities. Both problems are exacerbated when the cytologist is limited to a monolayer preparation of alcohol fixed cells, which limits the morphologic assessment of lymphoid populations and often precludes the use of ancillary techniques. FNA of lymph nodes provides many levels of information that may include classification of lymphomas. Although the importance of ancillary studies is increasingly emphasized, many lesions can be diagnosed by morphology alone, and appropriate morphologic evaluation and selection of material for testing is often necessary for meaningful molecular study results. Optimizing cytopathologic assessment of lymph node aspirates requires clinical correlation, scrupulous technique in acquiring and preparing samples and use of both Papanicolaou and Giemsa stains. Report nomenclature should indicate the level of information achieved and subsequent action required. Based on problems encountered and lessons learned over 20 years, this lecture will illustrate the cytologic features and diagnostic pitfalls of a full range of pathologies encountered in lymph nodes of the head and neck, including infections, noninfectious reactive lymphadenopathies, and primary and secondary neoplasms.

From University of Toronto, Toronto, Ontario, Canada.

JAPANESE SOCIETY OF CLINICAL CYTOLOGY SATELLITE MEETING: MOLECULAR CYTOPATHOLOGY

SS-12 MOLECULAR CYTOPATHOLOGY: INTRODUCTION

R. Osamura, H. Itoh and A. Serizawa

Molecular cytopathology (MCP) is defined as molecular studies applied on the cytologic specimen. MCP has been applied to detect specific organisms or oncologic changes at molecular levels. MCP is performed (1) on the cytologic specimens or (2) on DNA/RNA extracted from the cytologic smears. (1) MCP on the cytologic specimens includes in situ hybridization (ISH) and fluorescence ISH (FISH). FISH has been extensively used to detect oncogenic HPV DNA subtypes. We have experienced that FISH has been best applied on the cytologic specimens, that is, amplification, translocation or deletion. HER2 FISH has been successfully applied for trastuzumab therapy in breast cancers. (2) MCP on DNA/RNA extracted from the cytologic specimens has been applied to detect the molecular changes. Laser capture microdissection (LCM) is particularly helpful to pursue molecular changes on the morphologic basis. We have detected p53 mutation from the LCM-selected cells in breast cancers. cDNA microarray may also be attempted. These molecular techniques have been efficiently applied on liquid-based cytology (LBC). Cell blocks are expected to serve as prospective resources for molecular analysis. This JSCC Satellite Meeting focuses on molecular cytopathology, and the applications of various techniques will be presented.

From Department of Pathology, Tokai University School of Medicine, and Division of Diagnostic Pathology, Tokai University Hospital, Tokyo, Japan.

SS-13 MOLECULAR DIAGNOSTICS IN CERVICAL CANCER SCREENING

J. Lindner

OBJECTIVE: To discuss the application of new molecular diagnostic methods to the screening for cervical cancer and its precursor and prognostication of squamous intraepithelial lesions.

DISCUSSION: This lecture overviews the current literature describing the use of molecular diagnostic methods in cervical cancer screening. These markers fall into 2 broad categories: indicators of the present of human papillomavirus (HPV) infection and markers that HPV has altered the DNA synthetic pathway or cell cycle control of the cell. The use of molecular markers to assess cervical abnormalities has been pursued to achieve a variety of goals. Foremost has been the effort to clarify the diagnosis of cases that are of indeterminate abnormality after cytology review, so-called atypical squamous cells of undetermined significance (ASCUS). Of potential interest is the use of biologic markers that may provide prognostic information as to which, among the cases of low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL), have a greater probability to progress to significant lesions. This desire is prompted by interest in triaging cases into different patterns of clinical follow-up. To date, this has not been successful. In addition, molecular markers have been advocated as adjuncts to cytology to increase the sensitivity of cytologic diagnosis. These approaches include both HPV testing, and immunohistochemical analysis of cytologic samples. Finally, there is a school of thought that advocates molecular testing as a replacement for cytology-based screening. Assessment of the utility of these different approaches requires analysis of the parameters that influence test utility (sensitivity, specificity, positive predictive value and negative predictive value) in the context of cost effectiveness and evolving patient management guidelines. Further complicating an assessment of molecular markers is the continuing evolution of cervical cytology, including the improvements in liquid-based cytology and computer-assisted screening. Improvements provided by imaging-assisted cytology have continued advantages.

From Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A.

SS-14 CYTOMOLECULAR ANALYSIS OF NONGYNECOLOGIC LIQUID-BASED CYTOLOGY

N. Nemoto, Y. Nakanishi, K. Komatsu and T. Seki

Liquid-based cytology (LBC) was originally developed as a procedure of cell preparation for gynecologic specimens, and now it has been accepted widely in the gynecologic field. However, we disclosed that LBC procedure is also useful for nongynecologic cytology specimens such as fine needle aspirations (FNA), endoscopic brushings and scrapings, bronchioalveolar lavages and urine and other body fluids and so on. In this presentation, we will talk about cytomolecular analysis of nongynecologic specimens processed for LBC with or without laser assisted microdissection technique. LBC
preparations of the nongynecologic specimens (breast tumor scrapings, urine, body fluid) were processed for routine cytomorphologic examination and molecular analysis of HER-2, cytokeratins and p53. We also examined what was the influence of long-term storage of the specimens in the LBC preservatives on cell morphology and molecular analysis. On Papanicolaou-stained cytology examination, the LBC preparations were good enough to evaluate the cell morphology. In the molecular analysis, p53 mutation was satisfactorily demonstrated in the urine samples (about 50 tumor cells) by PCR-SSCP technique. In addition, cytokeratin mRNA and HER-2 mRNA were also satisfactorily detected in the cell samples, which were stored for more than 2 weeks in the preservative solutions of LBC. The HER-2 mRNA levels were well correlated with the expression of HER-2 protein and with HER-2 DNA levels demonstrated by 2-color FISH. In conclusion, LBC preparations would be a quite useful tool for both the cytologic evaluation and molecular analysis of nongynecologic cytology specimens.

From the Department of Pathology, Nihon University School of Medicine, and Pathology Division, Nihon University Itabashi Hospital, Tokyo, Japan.

SS-15 FEATURE ASPECTS OF CLINICAL CYTOLOGY IN LUNG NEOPLASMS: LUNG CANCER DIAGNOSIS BASED ON PROTEOMIC ANALYSIS AND DIGITAL SLIDE SCANNING


More than 20 years have passed since a consensus was reached that the only way to reduce lung cancer mortality is early detection. The detection of early-stage lung cancer has become increasingly frequent during this period. However, how does clinical cytology contribute to the early detection of lung cancer? The increase in the detection of early-stage lung cancer is mainly due to the development and spread of computed tomography, even though thorough cytology contributes to the early detection of central type early-stage lung cancer. We believe that several efforts are still needed for the clinical diagnosis of early stage lung cancer (1) technologies to obtain appropriate specimens from tiny lesions and (2) qualitative diagnosis of not only the biologic characteristics of the tumor cells but also morphologically differential diagnosis between benign and malignant tumors. Cytologic diagnosis reflecting the biologic tumor characteristics are needed for the determination of therapeutic strategies. We will introduce proteomic analysis to clarify biologic tumor characteristics in direct relation to therapeutic strategies. Some Japanese industrial companies have developed new technologies to realize digital slide scanning that can be applied to cytologic specimens. This system was originally developed for digital pathology, and converts a glass slide to a 1.9-gigapixel in high-resolution digital slide in approximately 3 minutes in standard mode (× 20 mode). When cytologic specimens are scanned, higher resolution images of 7.6 gigapixels (×40 mode) are required. Digital slide technologies will realize cytologic diagnosis without microscopy. Simultaneous observation using PC monitors by multiple screeners will enable more accurate cytoscreening without overlooking. Furthermore, rapid cytologic diagnosis at hospital with neither resident cytoscreeners nor cytologists can easily be realized. Another benefit of digital slides is slide storage. We will introduce a new technology of digital slide scanning for cytology.

From Department of Surgery, Tokyo Medical University, Tokyo, Japan.

INNOVATIVE ENDOMETRIAL SCREENING JSCE

SS-16 ENDOMETRIAL CYTOLOGY: USE IN DETECTING SMALL ENDOMETRIAL CANCEERS


OBJECTIVE: To find endometrial cancer in the early stages leads to good prognosis for patients. The purpose of our study is to know the accuracy of endometrial cytology in the diagnosis of small endometrial cancers compared with that of endometrial biopsy.

METHODS: From 1986 to 2006, 941 patients with endometrial cancer underwent operation in our hospital. Among them, we reviewed cytologic and histologic specimens of 122 small endometrial cancers with a tumor diameter <10 mm. For endometrial cytology, aspiration or brush method was performed. For histologic review, endometrial biopsies and operation materials were examined. To determine the tumor size, entire cut sections were made from all the operation materials. We classified small endometrial cancers into 2 groups: with hyperplasia (type I) and without hyperplasia (type II), respectively.

RESULTS: There were no big differences between type I and II cancers in patient background. In the type I group, the sensitivity of endometrial cytology and histology was 74% and 80%, respectively. In the type II group, the sensitivity of endometrial cytology and histology was 87% and 83%, respectively. Endometrial cytology, compared with histology, was more useful to detect small endometrial cancers when the tumor was localized in the uterine fundus. Among the type II group, carcinous and endometrioid grade 3 adenocarcinoma, which led to a poor prognosis, tended to be detected earlier by use of endometrial cytology rather than histologic examination.

CONCLUSION: This study demonstrated that endometrial cytology is useful for detecting small endometrial cancers.

From the Cancer Institute Hospital, Ariake, Tokyo, Japan.

SS-17 A REPORTING SYSTEM FOR ENDOMETRIAL CYTOLOGY


OBJECTIVE: To overcome the problems related to the preparation of endometrial cytologic specimens and to propose a reporting system for endometrial cytology.

METHODS: We defined the requirements for adequate endometrial cytologic specimens and reevaluated endometrial cytologic specimens using this definition. The problems related to the preparation of endometrial cytologic specimens were investigated.

RESULTS: Among the unsatisfactory specimens, a lack of clinical information was most frequently observed (79%), followed by insufficient collection of cell clusters (57%). With respect to the specimen preparation methods, the crushing method was not suitable for subsequent specimen review. Bloody backgrounds and distorted cells or cell clusters caused by air-drying need to be eliminated by using proper equipment and appropriate care.

CONCLUSION: The importance of providing adequate, correct clinical information for a cytologic diagnosis to be made must be
emphasized. To obtain high-quality specimens, proper equipment and appropriate care are required when sampling cells. Using an endometrial cytology reporting system allows a diagnosis to be made that is based on high-quality specimens and thus improves diagnostic accuracy.

From Suzuka General Hospital, Mie; Yamada Red Cross Hospital, Fukuoka-Prefecture; Cancer Institute Hospital, Ariake, Tokyo; Kurashiki Cyuo Hospital, Osaka; Saiseikai Noe Hospital, Osaka; and Mie University, School of Medicine, Mie, Japan.

SS-18  MOLECULAR CYTOLOGY FOR UTERINE CERVICAL NEOPLASIA

Human papillomavirus (HPV) is playing an important role in the etiology of cervical cancer. Technology of the detection of HPV DNA or of the gene products due to the HPV infection is explosively developing and spreading all over the world. Integration of the HPV genome was believed to be the consequence of up-regulation of viral genome followed by cervical cancer progression. It is now possible to determine the physical status of the HPV genome in cells exfoliated from the cervix by real-time polymerase chain reaction (PCR), as well as in biopsy specimens by in situ hybridization. The cyclin-dependent kinase inhibitor p16 protein plays an important role in regulation of the mammalian cell cycle. Overexpression of p16 protein has been observed in not only squamous cell neoplasia but also glandular neoplasia or small cell carcinomas in the cervix, and immunohistochemistry of p16 protein is therefore useful for cervical cancer screening. Therefore immunocytochemistry of p16 protein could be a powerful screening method combined with Pap smears. Since the volume of the premalignant lesion is too small to obtain enough tissue for Southern blot or Western blot analysis, the methods HPV DNA typing, real-time PCR, in situ hybridization and immunocytochemistry of p16 protein from the exfoliated cells can be used to examine the mechanism of progression of cervical cancer and are useful for selecting high-risk group for cervical cancer in patients with cervical intraepithelial neoplasia. Liquid-based cytology in cervical cancer screening is applied not only for the Pap test but also for molecular diagnosis. It is especially important to determine whether patients diagnosed with atypical squamous (glandular) cells or dysplasia progress to cervical cancer by use of such molecular diagnostic tools.

From Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo, Japan.

SS-19  CYTOLOGIC IN SITU METHODS IN MESOTHELIOMA DIAGNOSIS IN EFFUSIONS
A. Dejmek

In spite of the increasing number of immunocytochemical markers available for effusion cytology, the cyologic diagnosis of malignant mesothelioma in effusions remains a challenge, especially the differentiation of neoplastic from benign hyperplastic mesothelial cells. Modern molecular biology generates new methods and findings but is often applied to cell and tissue extracts. In situ methods, on the other hand, allow correlation to morphologic features and conclusions regarding heterogeneous and mixed populations. Telomerase activity is usually analyzed with the telomere repeat amplification protocol (TRAP). The enzyme is up-regulated in > 80% of malignant tumors and thus has potential as a marker of malignancy. However, telomerase activity has also been demonstrated in several types of proliferating benign cells and when conventional TRAP has been applied to effusions the sensitivities and specificities have varied. With TRAP in situ, we have demonstrated telomerase in a small proportion of benign mesothelial populations, but the activity was usually weaker than in malignant cells, including mesotheliomas, and thus quantification of the activity may be a way to define a cutoff value for malignancy. Time resolved fluorescence (TRF) Imaging has been used with various immunostains to quantify the amount of antigen present and can be used for this purpose. When applied to hTERT immunocytochemistry in effusions, the results indicate that the brightest fluorescence found in a single object is a suitable parameter to use. This same approach can be applied to new, potentially diagnostic “markers,” such as growth factors, adhesion molecules and proliferation-related antigens.

From the Department of Clinical Pathology and Cytology, Malmo University Hospital and Department of Laboratory Medicine, Malmo, Lund University, Sweden.

SS-20  APPLICATION OF MOLECULAR MARKERS IN CERVICAL CYTOLOGY
A. Cheung

Cervical cytology is widely recognized to be effective in the screening for cervical cancers. However, false positive and negative diagnoses still exist. Liquid-based cytology (LBC) preparations allow collection of exfoliated cervical cells in liquid buffer and preparation of thin-layer slides. Since the production of a liquid-based cervical smear uses only a fraction of the cells collected in buffer, the residual cells remaining in the vial are available for ancillary studies. Human papillomavirus (HPV) molecular testing performed on LBC cell residues is the most common ancillary test, enabling triage of management of women with atypical squamous cells of undetermined significance, primary screening and follow-up of patients with cervical neoplasia. Other than the HPV tests, cervical cytology samples also can be used for genetic and epigenetic studies such as mutation and promoter methylation analysis, as well as assessment of telomerase activity. The ploidy of epithelial cells and the expression of genetic markers can be assessed with an intact morphologic background by immunocytochemistry and in situ hybridization. The effects are particularly good in LBC. For instance, p16 immunostaining on LBC has been reported to have a high positive predictive value in detection of dysplastic or cancer cells. We believe that combined cytopathologic evaluation and application of molecular markers in cervical cytology is a promising option to facilitate reliable detection of cervical cancer. Moreover, equivocal diagnoses based on a single clinical collection can be minimized to reduce need for repeated patient appointments. The genetic and biologic mechanisms underlying the development of cervical cancer can also be better understood.

From the University of Hong Kong, Hong Kong, China.
SS-21  NEW MOLECULAR MARKERS AS PREDICTORS OF VIRAL EVENTS AND DISEASE OUTCOME IN HUMAN PAPILLOMAVIRUS (HPV)–ASSOCIATED CERVICAL CARCINOGENESIS: EXPERIENCE FROM THE HPV-PATHOGENESIS STUDY

K. Syrjänen

OBJECTIVE: Oncogenic human papillomaviruses (HPVs) are capable of contributing to the development of malignant phenotype in the uterine cervix by several different mechanisms, most of which seem to be closely interrelated. Because these molecular interactions are mediated by proteins, these complex molecular pathways can be explored by immunohistochemistry (IHC).

METHODS: In the ongoing HPV-PathogenISS project (Italy), we target the key molecular pathways (cell adhesion, invasion, angiogenesis and metastases, cellular receptors, cell proliferation, transcription regulation, cell cycle regulation, apoptosis, cell signaling) in cervical carcinogenesis using IHC-based strategies. A series of 320 archival samples, including 150 squamous cell carcinomas (SCCs) with complete follow-up data, and 152 CIN lesions (followed up by serial polymerase chain reaction [PCR] after treatment), were subjected to IHC staining for 13 biomarkers: p16INK4a, E-cadherin, MMP-2, TIMP-2, VEGF-C, nm-23 H1, 67-kD laminin receptor, PCNA, NF-κB, Topo-2a, telomerase, survivin, and ERK-1. Our aim is to assess whether these biomarkers might be useful in predicting any of the intermediate end-point markers of cervical carcinogenesis: the grade of CIN, HR-HPV type, clearance of the virus after treatment of CIN or prognosis of cervical SCC.

RESULTS: At this writing, results are available on all 13 biomarkers, reported in a series of 12 papers published during 2005–2006. Highly divergent molecular mechanisms neatly explain the different associations of these markers with the 3 outcomes and their performance indicators as predictors of the latter.

CONCLUSION: As the final step, all 13 biomarkers are analyzed by meticulous multivariate modeling. Apart from getting new insights in the molecular pathogenesis of HPV-associated cervical carcinogenesis, we anticipate disclosing the individual markers, a panel of markers, or an expression profile of any such marker panel that would have positive predictive value high enough to make it suitable as a screening tool for CC precursors.

From the Department of Oncology, Turku University Hospital, Turku, Finland.

AMERICAN SOCIETY OF CYTOPATHOLOGY SATELLITE SYMPOSIUM: CYTOPATHOLOGY QUALITY IMPROVEMENT MEASURES IN THE UNITED STATES

SS-22  CYTOPATHOLOGY CONTINUING EDUCATION IN THE UNITED STATES: PRESENT AND FUTURE DIRECTIONS

N. Young

This session is an overview of the types of cytopathology continuing education programs offered in the United States to fulfill both educational and regulatory needs. Advantages and disadvantages of different forums will be discussed and the challenges of implementing novel and large-scale operations, such as the glass slide interlaboratory comparison programs offered by major American patholo-

SS-23  THE REGULATORY FRAMEWORK FOR CYTOLOGY LABORATORY OPERATIONS

Shirley E. Greening

Abstract not available at the time of going to press.

From Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.

SS-24  QUALITY ASSURANCE AND THE CHALLENGE OF OBJECTIVE PERFORMANCE MEASURES

E. Cibas

How does one evaluate the performance of cytotechnologists and cytopathologists? Can reliable, objective measures of performance be extracted from existing quality control activities? This presentation will explore the “science” of quality control in cytology and the value of robust information systems, which provide us with new and potentially user-friendly opportunities. Objective measures for evaluating performance are, in fact, available from existing quality control activities. These include such measures as false negative rates (for detection skills), κ values (for agreement between cytotechnologists and pathologists), atypical squamous cells of undetermined significance to squamous intraepithelial lesion ratios (for uncertainty), and receiver operating characteristic curves (for accuracy). Software programs can greatly streamline calculation of these values, but up-front investment of time and effort is necessary to write programs if they are not available as standard features of laboratory information system.

From Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.

SS-25  CYTOPATHOLOGY PROFICIENCY TESTING IN THE UNITED STATES: THE HISTORY, PROBLEMS, CURRENT STATUS AND FUTURE DIRECTIONS OF A CONTROVERSIAL QUALITY IMPROVEMENT PROGRAM

T. Bonfiglio

Proficiency testing (PT) for gynecologic cytology practice has been a controversial topic in the United States since it was first mandated by the Federal Government as part of the 1988 Clinical Laboratory Improvement Act (CLIA88). This law followed the exposé published in the Wall Street Journal in 1987 regarding significant problems in some cytology testing laboratories. From the beginning, the development of a suitable proficiency test for gynecologic pathology was fraught with many problems, including numerous scientific and philosophic issues as well as questions about the valid-
program. The original idea for a program for the diagnosis of early cervical cancer in Cuba emerged in October 1967. By that time cervical cancer was nearly the leading cause of death by cancer in the female population in Cuba, with an incidence of more than 35 per 100,000 and a rate of mortality around 20 in 100,000. The initial plan was traced with the clear purpose to reduce the incidence of invasive cancer of cervix by early detection and its adequate treatment. In the last 38 years, the program developed with variable efficiency, covering a maximum of 75% of the female population at risk and reducing the cervical cancer rate to 7.4 per 100,000 women, the sixth cause of death by cancer in women in Cuba. A long run has elapsed since the initial work began; new concepts, new technologies and new classifications have been introduced and applied; new bases related to epidemiology, cytology and pathogenesis have been settled; but objectives remain the same: to achieve the early detection of carcinoma of cervix, its opportune and effective therapy and the reduction of deaths by this neoplasm.

From Hospital Hermanos Ameijeiras, Havana, Cuba.


I. Borrajero Martinez

The original idea for a program for the diagnosis of early cervical cancer in Cuba emerged in October 1967. By that time cervical cancer was nearly the leading cause of death by cancer in the female population in Cuba, with an incidence of more than 35 per 100,000 and a rate of mortality around 20 in 100,000. The initial plan was traced with the clear purpose to reduce the incidence of invasive cancer of cervix by early detection and its adequate treatment. In the last 38 years, the program developed with variable efficiency, covering a maximum of 75% of the female population at risk and reducing the cervical cancer rate to 7.4 per 100,000 women, the sixth cause of death by cancer in women in Cuba. A long run has elapsed since the initial work began; new concepts, new technologies and new classifications have been introduced and applied; new bases related to epidemiology, cytology and pathogenesis have been settled; but objectives remain the same: to achieve the early detection of carcinoma of cervix, its opportune and effective therapy and the reduction of deaths by this neoplasm.

From Hospital Hermanos Ameijeiras, Havana, Cuba.

THE LATIN AMERICAN CYTOLOGY SOCIETY SATELLITE SYMPOSIUM: ACHIEVEMENTS OF SCREENING FOR CERVICAL CANCER IN LATIN AMERICA

SS-26 ADENOCARCINOMA IN BRAZIL

Elias Fernando Miziara

Abstract not available at the time of going to press.

From Base Hospital of the Federal District, Brasilia, Brazil.

SS-27 DEVELOPMENT AND IMPLEMENTATION OF CERVICAL CANCER CONTROL PROGRAM IN EL SALVADOR

Lisseth Ruiz de Campos

Abstract not available at the time of going to press.

From Instituto del Cáncer de El Salvador and Hospital Nacional Rosales, San Salvador, El Salvador.

SS-28 EVALUATION OF CERVIX CANCER CONTROL PROGRAM OF SANTA CRUZ, BOLIVIA, 1994–2006

Edith Claros Mercado

Abstract not available at the time of going to press.

From SOLCA, Guayaquil, Ecuador.

The socioeconomic, technical and scientific development factors in Latin America force us to pose strategies in accordance with this reality, different from those in developed countries. We have developed an early detection and control of cervix cancer program based on putting the existing resources to best use, fortifying the primary care services’ resolving capacity and the protagonism of women in the bettering of the health system. The program is based on 7 polices, which are the pillars on which it stands: (1) epidemiologic focalization of screening; (2) guaranties on the quality of the cytology tests; (3) bettering of the primary attention services’ resolving capacity and the organization of the service by levels; (4) permanent education of human resources; (5) participation of the institutes in the sector; (6) evaluation of results and permanent quality control; and (7) promotion of the participation of mature women. The implementation of these polities has diminished the incidence of the cervix cancer by 25%. The achievements and errors of the program during the first 9 years are being analyzed.

From the Cytology Laboratory of Cervix Cancer Control Program, Bolivia.
SS-31 CERVICAL CANCER CONTROL IN CHILE: THE NATIONAL CYTOLOGY LABORATORY NETWORK

R. Prado

OBJECTIVE: Evaluate performance of the national cytology laboratory network as related to requirements of the Cervical Cancer Control Program in Chile.

METHODS: Laboratory organization was evaluated and results during the period 1993–2005 were analyzed.

RESULTS: Screening was performed at 22 laboratories nationwide, with a total capacity of 800,000 Pap smears annually. A national reference laboratory provides for external quality assurance and the maintenance of a uniform laboratory-based information system. A total of 772,621 Pap smears were reported during 2005, with a positive rate of 2.1%; atypical squamous cells of undetermined significance (ASCUS)/atypical glandular cells of undetermined significance (AGUS) 1.3%; satisfactory but limited by absence of transformation zone components 13.4%; unsatisfactory 3.9%. A total of 10,364 women had biopsies because of atypical and positive cytology or clinical suspicion of cervical neoplasia. Cytohistologic correlation was 67% for low-grade squamous intraepithelial lesion (LSIL), 73% for high-grade squamous intraepithelial lesion (HSIL), and 78% for combined HSIL and invasive cancer. Sensitivity and specificity (ASCUS+) were 90% and 60%, respectively. Coverage of the population at risk increased from 26% in 1990 to 66% in 2005. Mortality for cervix cancer decreased in the same period from 12 in 100,000 to 7 in 100,000.

CONCLUSION: The capacity of the cytology laboratory network is sufficient to cover 80% of the female population at risk, with a Pap test every 3 years. There is space to improve efficiency of conventional cytology by selecting the most adequate devices for cell collection and providing continuing education to professional and technical personnel involved in sample collection and screening. No consideration has been given as yet to alternative screening methods such as liquid-based cytology, the cost of which would increase 3–4 times the overall cost of the screening program.

From Preventive Oncology Center University of Chile, Santiago, Chile.

SS-32 IMPORTANT ISSUES IN THE ORGANIZATION AND EVALUATION OF CERVICAL CANCER CONTROL PROGRAMS

L. Fernández

Cervical cancer is preventable, but it is still the most common cancer among women in Central America and many South American countries. Incidence and mortality trends have declined in many European countries, the United States, Canada and others. Many of these changes are due to changes in hygiene habits and sexual and reproductive patterns, but the effect of organized screening programs is not negligible. In Latin America, prevention efforts have focused mainly on screening women with cytology (Pap smears) through family planning services and treatment for neoplastic lesions, but organized programs are not in practice frequently. Thus most of these programs have resulted in an inefficient use of resources with no impact on incidence and mortality from the disease. Several countries, namely Brazil, Chile, Costa Rica, Cuba, Ecuador, El Salvador and Peru, are working to improve the effectiveness of cervical cancer screening. Intermediate indicators to evaluate the program process are very useful, in order to correct deviations and to explain the lack of success: screening facilities; the designation of special laboratories to provide cytologic services; the mechanisms for processing of cytologic smears and the return of results in an adequate time interval; the definition of referral mechanisms for patients; the creation of treatment centers for early or late stage lesions; the creation of an information system that allows evaluation process are some of requirements for these programs. The quality of the cytology is a main determinant of a successful cervical cancer screening program. Laboratories should following international standards, and a laboratory quality control system should be in practice. The planning of management, supervision and systematic evaluation of the program is an important contributor. The collaboration with the cancer registry and mortality system is essential to have main indicators of results and impact of the program.

From National Oncology Institute, Havana, Cuba.

PLATFORM PRESENTATIONS

HUMAN PAPILLOMAVIRUS (HPV)

A-01 A PEER COMPARISON PROGRAM FOR THE QUALITY ASSURANCE OF HPV DNA DETECTION USING THE DIGENE HYBRID CAPTURE II/SUREPATH METHOD SHOWS EXCELLENT ANALYTIC INTERLABORATORY CORRELATION

D. Kuebler, A. Illingworth, A. Blenc and D. Wilbur

OBJECTIVE: Interlaboratory peer comparison programs are a CLIA-mandated and national quality assurance activity in the clinical laboratory. No commercial program is currently available specifically designed for cytology laboratories performing HPV DNA (and no other types of viral) testing. We report the results of a self-developed program between 2 cytology laboratories.

MATERIALS AND METHODS: Between 4 and 11 SurePath (TriPath) liquid-based cervical cytology samples are selected at each of the 2 participating laboratories each quarter and exchanged without accompanying patient information. Samples are selected to test both positive and negative HPV DNA results in roughly equivalent numbers. Samples are run with the Hybrid Capture II (Digene) method using each laboratory’s standard procedure. The results are compared with the originating laboratory’s result. Statistics on correlation are compared on an ongoing basis as a method to assess each laboratory’s analytic performance.

RESULTS: Over a 3-year period, 12 exchanges took place, constituting 113 total specimens. Overall, there were 9 exchanges (76 specimens) showing 100% correlation and 3 exchanges (37 specimens) showing a total of 4 discordant results. Overall, this represents a 97% (109 of 113) correlation of results between laboratories. All 4 discordant cases were reported as negative by the original laboratory and positive by the exchange laboratory (2 in each direction).

CONCLUSION: The interlaboratory peer comparison result of 97% concordance shows excellent analytic agreement between the HPV DNA detection procedures of each laboratory. All discordant cases were “negative to positive” and were distributed equally by originating laboratory. The procedure is easily set up and provides assurance to each laboratory of ongoing performance for the detection of the HPV DNA anayte.

From Massachusetts General Hospital, Boston, Massachusetts; and Dahl-Chase Diagnostic Services, Bangor, Maine, U.S.A.