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The **C**ruix

BIMONTHLY FORUM FOR THE LABORATARIANS

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Editorial

We have in one of our previous issues dealt with a female genital cancer that afflicts large number of women worldwide (cervical cancer). In this issue we take up prostatic cancer and present to you all clinico-diagnostic aspects in ample depth. This is a slow growing cancer. The cancer cells may metastasize from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease. Rates of detection of prostate cancers vary widely across the world, with South and East Asia detecting less frequently than in Europe, and especially the United States. Prostate cancer tends to develop in men over the age of fifty and although it is one of the most prevalent types of cancer in men, many never have symptoms, undergo no therapy, and eventually die of other causes. This is because cancer of the prostate is, in most cases, slow-growing, symptom-free, and since men with the condition are older they often die of causes unrelated to the prostate cancer, such as heart/circulatory disease, pneumonia, other unconnected cancers, or old age. Many factors, including genetics and diet, have been implicated in the development of prostate cancer. The presence of prostate cancer may be indicated by symptoms, physical examination, prostate specific antigen (PSA), or biopsy and by PSA tests on blood samples. PSA and free PSA are important tumour markers for prostatic cancer. Suspected prostate cancer is typically confirmed by taking a biopsy of the prostate. Further tests, such as CT scans and bone scans, may be performed to determine whether prostate cancer has spread. DISEASE DIAGNOSIS outlines all aspects as related to cancer of the prostate.

INTERPRETATION talks about aminoacidurias and interpreting urine tests for inborn errors of metabolism. Though practised routinely in the western world, the appropriate tests are not carried out in the subcontinent as a matter of routine.

TROUBLE SHOOTING segment discusses a rather controversial issue – What happens when a laboratory makes large scale errors! Extensive use of automation in the clinical laboratory creates the potential for systematic errors that affect a large number of patient results before the error is discovered. What to do when such errors take place is presented in this issue.

BOUQUET is laced with photomicrographs of a few RBC disorders under Brain Teasers, few one liners given under In Lighter Vein will brighten up your mood, while a few phrases of wisdom are there under Wisdom Whispers. Happy reading.

PUBLISHED FOR THE TULIP GROUP CUSTOMERS

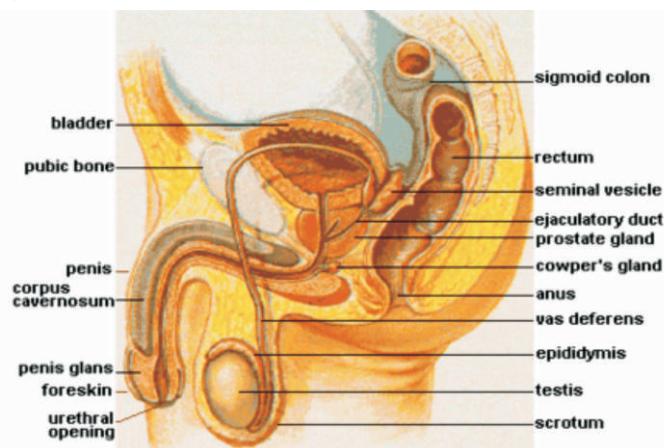
F O R P R I V A T E C I R C U L A T I O N O N L Y

DISEASE DIAGNOSIS

PROSTATE CANCER

INTRODUCTION: Prostate cancer is the most common noncutaneous cancer among males. Lung and bronchial cancer account for 37% of cancer-related death in males; prostate and colon cancers account for another 10% each. The diagnosis and treatment of prostate cancer continue to evolve. With the development of prostate-specific antigen (PSA) screening, prostate cancer is being diagnosed earlier in the disease course. Although prostate cancer can be a slow-growing cancer, thousands of men die of the disease each year. Education is important to help men understand the risk of progression and the various treatment options. This article provides a current overview of the biology, pathology, diagnostic techniques, natural history, and screening of this disorder.

RELEVANT ANATOMY: The prostate lies below the bladder and encompasses the prostatic urethra. It is surrounded by a capsule and is separated from the rectum by a layer of fascia termed the Denonvilliers aponeurosis.



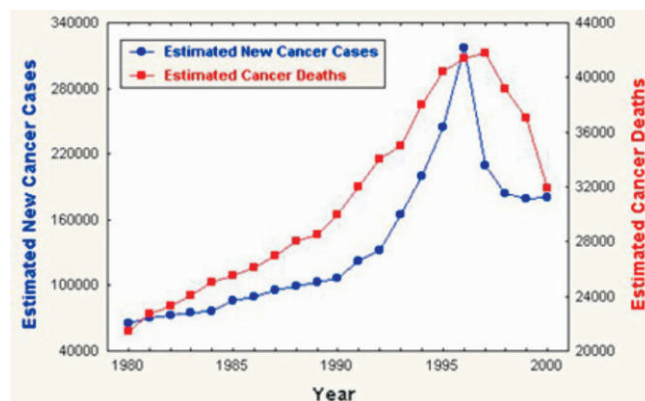
Relevant anatomy of the male pelvis and genitourinary tract.

The blood supply to the base of the bladder and prostate is from the inferior vesical, which is derived from the internal iliac. The capsular branches of the inferior vesical artery help identify the pelvic plexus arising from the S2-S4 and T10-T12 nerve roots. The **neurovascular** bundle lies on either side of the prostate on the rectum. It is derived from the pelvic plexus and is important for erectile function.

ETIOLOGY: **Race:** African American men have a higher prevalence and more aggressive prostate cancer than white men, who, in turn, have a higher prevalence than men of Asian origin. Studies have found that young African American men have testosterone levels that are 15% higher than in young white men. Furthermore, evidence indicates that 5-alpha reductase may be more active in African Americans than in whites, implying that hormonal differences may play a role. The independent contribution of race alone is difficult to qualify when the effects of health care access, income, education, and insurance status are also considered. **Diet:** A high-fat diet may lead to increased risks, while a diet rich in soy may be protective. These observations have been proposed as reasons for the low prevalence of this cancer in Asia. Rates of prostate cancer are much greater in Japanese American men than in native Japanese men, supporting the association of a high-fat diet with cancer. Cell culture studies have shown that omega-6 fatty acids are positive stimulants of prostate cancer cell growth, while omega-3 fatty acids are negative stimuli. These fats may exert their effects by alterations of sex hormones or growth factors or through effects on 5-alpha reductase. **Soy seems** to decrease the growth of prostate cancer cells in mouse models; however, apart from epidemiologic factors, no direct

evidence supports a beneficial effect in humans. Vitamin E may have some protective effects because it is an antioxidant. Decreased levels of vitamin A may be a risk factor because this can promote cell differentiation and stimulate the immune system. Vitamin D deficiency was suggested as a risk factor, and studies show an inverse relationship between ultraviolet exposure and mortality rates for prostate cancer. However, a specific correlation between 1,25-dihydroxyvitamin D levels and palpable disease, well-differentiated tumors, or mortality is inconclusive. **Selenium** may have a protective effect based on epidemiologic studies and is also believed to extend its effect via its antioxidant properties. **Hormones:** Hormonal causes have also been postulated. Androgen ablation causes a regression of prostate cancer. In addition, as indirect evidence of hormonal causes, eunuchs do not develop adenocarcinoma of the prostate. **Hsing and Comstock** performed a large study comparing patients with prostate cancer with controls and found no difference in levels of testosterone, dehydrotestosterone, prolactin, follicle-stimulating hormone, or estrone. **The Prostate Cancer Prevention Trial** studied the prevalence of prostate cancer between a control group and a group given a 5-alpha-reductase inhibitor (finasteride). While the 5-alpha reductase inhibitor appeared to decrease the prevalence of tumors, those that did arise appeared histologically more aggressive. Only long-term follow-up of these patients will determine whether this more aggressive histology accurately reflects the underlying biology of these tumors or whether it is an artifact of the treatment. **The Expert Panel** concluded that asymptomatic men with a PSA level of less than 3 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-alpha-reductase inhibitors for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer). Men who are taking 5-alpha-reductase inhibitors for benign conditions, such as lower urinary tract (obstructive) symptoms (LUTS), may benefit from a similar discussion; these patients should understand that the improvement of LUTS relief should be weighed with the potential risks of high-grade prostate cancer from 5-alpha-reductase inhibitors (although most of the Panel members judged the risk of high-grade prostate cancer to be unlikely). A reduction of approximately 50% in PSA level by 12 months is expected in men taking a 5-alpha-reductase inhibitor; however, because these changes in PSA may vary among men, and within individual men over time, the Panel has no recommendations for a specific cut point to trigger a biopsy for men taking a 5-alpha-reductase inhibitor. No specific cut point or change in PSA level has been prospectively validated in men taking a 5-alpha-reductase inhibitor.

FREQUENCY: With the advent of PSA screening, a greater number of men require education about prostate cancer and how it is diagnosed, staged, and treated so they can select the most appropriate treatment. **Prostate cancer** is rarely diagnosed in men younger than 40 years, and it is uncommon in men younger than 50 years.



Estimated incidence and mortality from prostate cancer.

Prevalence rates of prostate cancer remain significantly higher in African American men than in white men, while the prevalence in Hispanic men is similar to that of white men. Hispanic men and African American men present with more advanced disease, most likely related to external (eg, income, education, insurance status) and cultural factors. In addition, African American men generally have higher levels of testosterone, which may contribute to the higher incidence of carcinoma. **Between 1989 and 1992**, incidence rates of prostate cancer increased dramatically, probably because of earlier diagnoses in asymptomatic men as a result of the increased use of serum PSA testing. In fact, the incidence of organ-confined disease at diagnosis has increased because both PSA testing and standard DRE are performed. **Prostate cancer** is also found during autopsies performed following other causes of death. The rate of this latent or autopsy cancer is much greater than that of clinical cancer. In fact, it may be as high as 80% by age 80 years. **The prevalence of clinical cancer** varies by region, and these differences may be due to some of the genetic, hormonal, and dietary factors discussed in Etiology. High rates are reported in northern Europe and North America, intermediate rates are reported in southern Europe and Central and South America, and low rates are reported in Eastern Europe and Asia. **Interestingly**, the prevalence of the latent or autopsy form of the disease is similar worldwide. Together with migration studies, this suggests that environmental factors, such as diet, may play a significant promoting role in the development of a clinical cancer secondary to a latent precursor.

SYMPTOMS: Local Symptoms: In the pre-PSA era, patients with prostate cancer commonly presented with local symptoms. Urinary retention developed in 20-25% of these patients, back or leg pain developed in 20-40%, and hematuria developed in 10-15%. Currently, with PSA screening, patients report urinary frequency (38%), decreased urine stream (23%), urinary urgency (10%), and hematuria (1.4%). However, none of these symptoms is unique to prostate cancer and each could arise from various other ailments. Forty-seven percent of patients are asymptomatic.

Metastatic Symptoms: Metastatic symptoms include weight loss and loss of appetite; bone pain, with or without pathologic fracture (because prostate cancer, when metastatic, has a strong predilection for bone); and lower extremity pain and edema due to obstruction of venous and lymphatic tributaries by nodal metastasis. Uremic symptoms can occur from ureteral obstruction caused by local prostate growth or retroperitoneal adenopathy secondary to nodal metastasis.

PATHOPHYSIOLOGY AND NATURAL HISTORY: Pathophysiology: Prostate cancer develops when the rates of cell division and cell death are no longer equal, leading to uncontrolled tumor growth. Following the initial transformation event, further mutations of a multitude of genes, including the genes for p53 and retinoblastoma, can lead to tumor progression and metastasis. Most (95%) prostate cancers are adenocarcinomas. **Approximately** 4% of cases of prostate cancer have transitional cell morphology and are thought to arise from the urothelial lining of the prostatic urethra. Few cases have neuroendocrine morphology. When present, they are believed to arise from the neuroendocrine stem cells normally present in the prostate or from aberrant differentiation programs during cell transformation. **Of prostate cancer cases**, 70% arise in the peripheral zone, 15-20% arise in the central zone, and 10-15% arise in the transitional zone. Most prostate cancers are multifocal, with synchronous involvement of multiple zones of the prostate, which may be due to clonal and nonclonal tumors. **Natural history:** The natural history is still relatively unknown, and many aspects of progression are poorly understood. Symptoms or abnormal DRE findings in the pre-PSA era brought only 40-50% of patients with prostate cancer to medical attention, and these patients usually had locally advanced disease. The advent of PSA testing has helped to identify patients with less-advanced, organ-confined disease. **In fact**, the pendulum has shifted to the point that certain members of the urologic community feel that active surveillance, also known as expectant management, may have a role. A study confirms that mortality rates due to tumors with a Gleason score of 2-

4 was less than 7%. Urologists advocate active surveillance in patients with a PSA density of less than 0.1 ng/mL, with no adverse pathologic findings on needle biopsy, and with tumors with a Gleason score of 6 that are smaller than 3 mm. **Evidence** suggests that most prostate cancers are multifocal and heterogeneous. Cancers can start in the transitional zone or, more commonly, the peripheral zone. When these cancers are locally invasive, the transitional-zone tumors spread to the bladder neck, while the peripheral-zone tumors extend into the ejaculatory ducts and seminal vesicles. Penetration through the prostatic capsule and along the perineural or vascular spaces occurs relatively late. **The mechanism** for distant metastasis is poorly understood. The cancer spreads to bone early, occasionally without significant lymphadenopathy. Currently, 2 predominant theories have been proposed for spread—the mechanical theory and the seed-and-soil theory. **The mechanical theory** involves direct spread through the lymphatics and venous spaces into the lower lumbar spine. **Advocates** of the seed-and-soil theory believe that tissue factors that allow for preferential growth in certain tissues, such as the bone, must be present. Lung, liver, and adrenal metastases have also been documented. Specific tissue growth factors and extracellular matrices are possible examples. **The doubling time** in early-stage disease is as slow as 2-4 years, but this changes as the tumor grows and becomes more aggressive. Larger tumors usually have a higher Gleason grade and a faster doubling time.

INCIDENTAL FINDINGS: In the modern era, most patients present because of abnormalities in a screening PSA level or findings on digital rectal examination (DRE) rather than because of symptoms. However, prostate cancer can be an incidental pathologic finding when tissue is removed during transurethral resection to manage obstructive prostatic symptoms.

Elevated prostate-specific antigen level: PSA is a single-chain glycoprotein that has chymotrypsinlike properties. PSA slowly hydrolyzes peptide bonds, thereby liquifying semen. The upper limit of normal for PSA is 4 ng/mL. Some advocate age-related cutoffs, such as 2.5 ng/mL for the fifth decade of life, 3.5 ng/mL for the sixth decade of life, and 4.5 ng/mL for the seventh decade of life. Others advocate race-specific reference ranges. Using recent data from screening studies, some have advocated upper limits of normal of 2.5 ng/mL instead of 4 ng/mL. **Prostate-specific antigen velocity:** PSA velocity is an important concept. A PSA velocity of lower than 0.75 ng/mL/y has traditionally been used to prompt a prostate biopsy. However, recent data suggest that, among men younger than 50 years, a PSA velocity of 0.6 ng/mL/y may be more appropriate. **Percent of free prostate-specific antigen:** The measurement of bound and free PSA is a recent development that can help to differentiate mildly elevated PSA levels due to cancer from elevated levels due to benign prostatic hyperplasia. The lower the ratio of free-to-total PSA, the higher the likelihood of cancer. Free PSA is reported as a percentage. For example, among men with greater than 25% free PSA, only 8% are found to have cancer at prostate biopsy. In contrast, more than half of men with less than 10% free PSA are found to have cancer at biopsy. While cutoffs may be used, the percentage of free PSA is usually used as an additional factor in making an informed recommendation for or against biopsy. Generally, these percentages are useful in patients who have a PSA level in the range of 4-10 ng/mL. **This information** is most useful in men with very large glands or in men in whom one biopsy result has already been negative. In healthy men with a PSA level of 4-10 ng/mL, many recommend biopsy without the additional free-PSA test or consider a trial of antibiotic therapy for 4-6 weeks before repeating the PSA test. If antibiotic therapy quickly lowers the PSA level to within the reference range, the cause of the prior elevation is less likely to be prostate cancer, and the PSA test should be repeated within a few months.

Abnormal digital rectal examination findings: Various factors are considered when a DRE is performed. A nodule is important, but findings such as asymmetry, difference in texture, and boggy areas are important clues to the patient's condition and should be considered in conjunction with the PSA level. Change in texture over time can offer important clues about the

need for intervention. Cysts or stones cannot be accurately differentiated from cancer based on DRE findings alone; therefore, maintain a high index of suspicion if the DRE results are abnormal. In addition, if cancer is detected, the DRE findings form the basis of clinical staging of the primary tumor (ie, tumor [T] stage in the tumor node metastases [TNM] staging system). In current practice, the DRE results are normal but the PSA readings are abnormal in most patients diagnosed with prostate cancer.

NATURAL HISTORY BY STAGE: T1a - Progression over 10 years (uncommon), T1b - Tumor-related death rate of 10% in 10 years, T2 - Ten-year metastasis-free survival rate of 81% with grade 1, 58% with grade 2, and 26% with grade 3, T3 - Lymph node metastasis at presentation in 50% and approximately 25% rate of 10-year disease-free survival. The natural history of clinically localized disease varies, with lower-grade tumors having a more indolent course, while some high-grade lesions progress to metastatic disease with relative rapidity. Several studies have examined the cancer-specific and quality-of-life outcomes associated with a watchful-waiting approach to localized disease. Prostate cancer mortality increased from 15 deaths per 1000 person-years during the first 15 years to 44 deaths per 1000 person-years beyond 15 years of follow-up. Taken together, these data suggest that, although most prostate cancers diagnosed at an early stage have an indolent course, local tumor progression and aggressive metastatic disease may develop in the long term. In addition, these findings would support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.

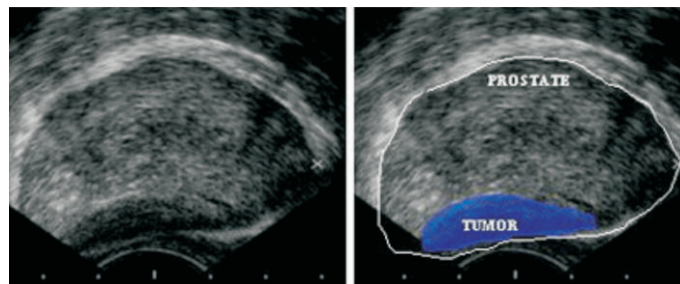
SCREENING: DRE and PSA evaluation are the 2 components necessary for a modern screening program. Transrectal ultrasonography (TRUS) has been associated with a high false-positive rate, making it unsuitable as a screening tool, although it is very useful for directing prostatic biopsies. The indications for screening are controversial. The American Cancer Society recommends that both PSA evaluation and DRE should be offered annually, beginning at age 50 years, to men who have at least a 10-year life expectancy and to high-risk younger men. Information should be provided to patients regarding potential risks and benefits of intervention. Despite the apparent survival advantage of early diagnosis conferred by PSA screening, a recent study recommends against screening for prostate cancer in men aged 75 years or older. The statement also concludes that, currently, the balance of benefits versus drawbacks of prostate cancer screening in men younger than age 75 years cannot be assessed because of insufficient evidence. Advocates of screening believe that early detection is crucial to finding organ-confined disease and to reducing the likelihood of mortality. When symptoms develop or when DRE results become positive, most cases have already advanced beyond organ-confined disease. Those who do not advocate screening worry that screening will detect cancers that are not biologically significant (ie, in patients who will die with prostate cancer rather than from it). Currently, age-specific PSA cutoffs are used to guide screening. The trend is toward lowering the threshold level to 2.5 ng/mL, but this has not yet been widely accepted. Men who choose to undergo screening should begin at age 50 years. Men in high-risk groups, such as African Americans and those with a strong familial predisposition (2 or more affected first-degree relatives), should begin screening at a younger age (40-45 y). These men are less likely to have the latent form of the disease and benefit from treatment. More data on the precise age to start prostate cancer screening are needed for men at high risk. Recent data from international studies suggest that mortality rates are lower as a result of PSA screening. These beneficial effects are likely due to the fact that treatment rather than observation may enhance disease-specific survival. Other theories have been proposed to account for the decrease, and these include changing treatment practices and artifacts in mortality rates secondary to the changing incidence.

ABNORMAL RECTAL EXAMINATION FINDINGS: Findings from the DRE are crucial. An irregular firm prostate or nodule is typical, but many cancers are found in prostates that feel normal. Pay careful attention to the prostate

consistency, along with the seminal vesicles and adjacent organs, to detect spread of the disease to these structures.

Overdistended bladder due to outlet obstruction. Neurologic findings secondary to cord compression: Other subtle findings, such as paresthesias or wasting, are uncommon. Lower extremity lymphedema. Supraclavicular adenopathy. Lower extremity deep venous thrombosis. Cancer cachexia.

TRANSRECTAL ULTRASONOGRAPHY: TRUS is used to examine the prostate for hypoechoic areas, which are commonly associated with cancers but are not specific enough for diagnostic purposes. At least 6 or, more recently, 10 or more systematic biopsy specimens of peripheral and, occasionally, transitional zones are taken under ultrasonographic guidance. Samples should include most areas of the gland, irrespective of ultrasonographic abnormalities.



Transrectal sonogram of the prostate showing a hypoechoic lesion in the peripheral zone of the gland that is suggestive of cancer.

DIFFERENTIAL DIAGNOSES: Benign prostatic hypertrophy, Calculi, Prostatic cysts, Prostatic tuberculosis, Prostatitis.

FUTURE AND CONTROVERSIES: Whether one of the several different modalities used for treating localized prostate cancer offers survival benefits over another remains controversial. The choice of definitive therapy has been suggested to make a significant difference in long-term survival in less than 10% of patients. This means that most patients are either cured by any definitive therapy or present with incurable disease that cannot be detected, and, ultimately, any treatment modality fails to be curative. A 2008 research summary by the Agency for Healthcare Research and Quality (AHRQ) concluded that no single therapy can be considered as the preferred treatment for presumed organ-confined prostate cancer. The AHRQ based this conclusion partly on the lack of data regarding efficacy and partly on the concept that differences in adverse effects, convenience, and costs among the available therapies may be important factors in the choice of treatment in an individual patient. The AHRQ noted that, although all treatment options carry adverse effects, patient satisfaction with therapy is high.

MOLECULAR PROGNOSTIC MARKERS: Over the past few years, several molecular markers have been shown to aid in the prognostication of patients undergoing treatment for localized and metastatic prostate cancers. Assessment of the molecular alterations or gene products of TP53, RB, BCL2, cathepsin-D, CDH1, and PTEN, among many others, have been reported. Prospective trials are needed to assess these markers more thoroughly before their implementation in current management is recommended.

REVERSE TRANSCRIPTASE-POLYMERASE CHAIN REACTION: Reverse transcriptase-polymerase chain reaction (RTPCR) testing may be able to find very small amounts of PSA nucleic acid in the blood stream, prostatic fossa, or bone marrow. In the future, this may be helpful in determining which patients have residual tumor following surgery (RTPCR-positive prostate fossa) or a higher rate of tumor recurrence (RTPCR-positive lymph nodes at surgery or persistently positive bone marrow samples months after treatment).

TROUBLESHOOTING

LARGE SCALE LAB ERRORS

Extensive use of automation in the clinical laboratory creates the potential for systematic errors that affect a large number of patient results before the error is discovered. When a large-scale testing error is found, the approaches recommended for responding to individual medical mishaps are often inadequate. This report uses 2 case studies to illustrate some of the unique challenges facing laboratory managers confronted with a large-scale testing error. 9 distinct constituencies have been identified that may be impacted by large-scale testing errors, each of which requires laboratory management's thoughtful and timely attention.

Introduction

In October 2008, Quest Diagnostics (QD) initiated what may have been the largest recall of clinical test results, due to a systematic laboratory error that potentially affected more than 300,000 vitamin D values.[1] According to a company spokesperson, 7% of vitamin D tests performed by QD from early 2007 to mid 2008 were impacted by incorrect calibrators used at 4 of 7 QD testing facilities. Because of the controversial usefulness of vitamin D testing in patient management, it was not clear whether any patients were harmed as a result of testing inaccuracy. Although the QD recall and retesting program received national publicity, in our experience large-scale testing errors involve many (possibly most) testing facilities. Laboratories with the most highly developed quality management systems may, ironically, be most adept at identifying systematic errors that pass undetected at less capable facilities. Much has been written about how to respond to errors in health care. Professional societies have advocated discussion of a serious error with the affected patient and the assumption of responsibility. One hospital accrediting organization, The protocols require use of a specific investigatory technique called "root cause analysis" to examine "sentinel events" associated with certain types of serious errors and to address latent causes that can lead to recurrence of problems. The extensive use of automation and other mass-production techniques in the clinical laboratory creates the potential for systematic errors to affect a large number of patient results before the error is discovered. The term "large-scale testing error" is used to mean an error that impacts a large number of clinical laboratory results because of a defect in a system used for high-volume testing. Large-scale testing errors differ from the type of errors that most commonly occur in other health care settings. Most health care errors are one-of-a-kind or rare events that require some individual caregiver's cognitive failure—a slip, lapse, or mistake—usually in concert with other factors. When a large-scale testing error is found, the approaches recommended for responding to individual medical mishaps are often inadequate. Patients potentially impacted by a large-scale testing error may not be immediately identifiable or easily contacted and often number in the thousands. The clinical impact of the error is likely to be incompletely understood at the time the error is discovered, clouding decisions about whether and how to notify caregivers and patients. Finally, large-scale testing errors are likely to be ongoing at the time a laboratory problem is first detected, with additional errors being produced every day. Post discovery investigatory techniques used to study isolated errors, such as root cause analysis, are generally conducted over the course of several weeks during what is assumed to be a safe window in which the error in question is unlikely to recur. When large-scale testing errors are discovered in the laboratory, the potential for additional ongoing damage must be addressed immediately, often before root causes of the error are fully illuminated. This report uses 2 case studies to illustrate some of the unique challenges facing laboratory managers confronted with a large-scale testing error. We use these cases as a springboard for discussing 9 distinct constituencies that may be impacted by large-scale testing errors, each of which requires laboratory management's thoughtful and timely attention.

Table 1.

Constituency	Responsibility
Patients about to undergo testing	Prevent additional errors
Patients who have undergone testing	Assess risk of adverse consequences; notify and correct results or offer retesting as appropriate
Caregivers and other customers	Assess risk of adverse consequences; notify and correct results or offer retesting as appropriate
Payers	Reverse charges for results known or likely to be inaccurate
Regulators and accreditors	Notify of incident as appropriate or required; cooperate in investigation and industry notification as required
General public	Proactive communication of any ongoing risk to public health and safety
Vendors and suppliers	Notify of incident; cooperate in investigation of cause as required
Laboratory owners	Notify of incident; assist with vulnerability assessment and communication
Laboratory workers	Notify of incident; define authorized communication channels for responding to incident; assess risk to laboratory staff and follow up as appropriate

Example 1. Incorrect International Normalized Ratio Results

In 2007, during a certification inspection of Laboratory X, an inspector attempted to verify the laboratory's international normalized ratio (INR) calculation using the laboratory's measured prothrombin time (PT), mean normal PT, and the labeled International Sensitivity Index (ISI) of the manufactured prothrombin reagent. The INR value manually calculated by the inspector was found to be 8% greater than the INR reported by the analyzer that had measured the PT. Manually calculated INR values for 2 more PTs were also greater than the INR reported by the analyzer. The inspector cited the laboratory for a deficiency, and the analyzer in question was immediately taken out of service while the problem was investigated. Investigation the day after the inspection revealed that the analyzer had been calibrated 2 months before the inspection. Although the reagent ISI had been correctly entered into the coagulometer at the time of calibration, examination of calibration records showed that an additional "adjustment ratio" had not been calculated and entered into the analyzer, as required by a technical bulletin issued by the instrument manufacturer. Instead, the adjustment ratio that had been calculated and entered during an earlier calibration remained in the instrument. The laboratory's written recalibration procedure included instructions to enter the adjustment ratio, but this step had been omitted during the most recent calibration. The technologist who performed the calibration was experienced with coagulation testing and calibration but recently had been transferred from another laboratory within the health care system that used a different model coagulometer produced by the same manufacturer. The model with which the technologist was familiar did not require entry of the adjustment ratio. As a result of the omission during calibration, all INR values calculated by the coagulometer since the recalibration were 8% lower than what they would have been if the correct ratio adjustment factor had been entered during the calibration procedure. No proficiency testing events had occurred during the 2 months between the coagulometer recalibration and the inspection of Laboratory X. On the day after the inspection, the analyzer was recalibrated using the appropriate adjustment ratio. Ten samples were run on the analyzer, the INR was manually calculated for each sample, and all reported results were in agreement with manual calculations. The instrument was then placed back in clinical service. Laboratory X served a large outpatient facility but no

inpatients. The laboratory was cited for a total of 6 deficiencies as a result of the inspection. The other 5 deficiencies concerned process issues that did not directly impact the accuracy of test results. The laboratory medical director was aware of all 6 citations and tasked the laboratory technical director with documenting corrective action that had been taken in relation to each deficiency. Three weeks after the inspection, a representative from the Laboratory Accreditation Program called the technical director and inquired into the specific steps that the laboratory had taken to notify caregivers about erroneous INR results. After receiving the call, the laboratory's medical and technical directors organized a "look-back" program to address erroneous results that had been released. A search program was developed using the ad hoc query language that formed part of Laboratory X's laboratory information system. The search revealed that 1,620 INR values had been reported by the coagulometer since its last calibration. Each of the 1,620 reported INR results were presumed to be 8% lower than the value that would have been reported had the instrument calibration been performed correctly. A computer program was then written to generate letters to each physician who had ordered an implicated assay. Each physician was informed of the names of impacted patients, the incorrectly reported INR value, and the correct value. To facilitate follow-up, patients and their INR results were divided into 3 groups: (1) patients with values that were reported as subtherapeutic (INR < 1.5) but that were actually therapeutic (INR between 1.5 and 3); (2) patients with values that were reported as therapeutic but that were actually supratherapeutic (INR > 3); and (3)

patients with values that when corrected did not cross from one category to another. Of the implicated results, 93% fell into this third group (no change in category). Caregivers were given lists of their patients who fell into each category. The risk management department of the hospital system associated with the laboratory was contacted, as was executive management of the hospital. Six days elapsed before the risk management department cleared for release a letter from the laboratory describing the nature and cause of the problem. This letter was sent to all physicians who had ordered 1 of the 1,620 assays, along with a list of corrected results. Retesting at no charge was offered to all impacted patients, and physicians were encouraged to contact the laboratory if they believed any patient had experienced an adverse event as a result of the error. No communications about adverse events were received. Because letters informing physicians about the erroneous test results were released approximately 5 weeks after the error was discovered, many patients involved by the incident had already been retested as part of routine monitoring of oral anticoagulant therapy. Approximately 20 patients and their caregivers availed themselves of the offer for follow-up testing at no charge. All charges related to the 1,620 incorrectly reported test results were reversed. A sentinel event investigation was initiated that identified the use of multiple models of coagulometers within the health care system as a causal factor for the incident, and the model that required manual entry of the ratio adjustment was replaced approximately 6 months after the sentinel event investigation concluded.

To be continued.

BOUQUET

In Lighter Vein

One liners

- Some tortures are physical...And some are mental,..But the one that is both...ls dental.
- Hardware: the parts of a computer that can be kicked
- Sign in a bar: Those drinking to forget, please pay in advance
- When a women cancels a date u should know that she has to ...When a man cancels a date you should know that he has two.
- I was born to be a pessimist. My blood type is B Negative
- My wife and I were happy for twenty years. Then we met.
- I saw a woman wearing a sweat shirt with "Guess" on it. So I said "Implants?"
- My girlfriend told me I should be more affectionate. So I got two girlfriends.
- Behind every successful man, there is a woman And behind every unsuccessful man, there are two.
- We always hold hands. If I let go, she shops.
- A good wife always forgives her husband when she's wrong.
- The secret of a happy marriage remains a secret.
- When a man steals your wife, there is no better revenge than to let him keep her.
- I haven't spoken to my wife in 18 months - I don't like to interrupt her.

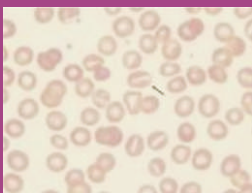
Wisdom Whispers

- Never tell your problems to anyone...20% don't care and the other 80% are glad you have them.
- Have you ever wondered which hurts the most: saying something and wishing you had not, or saying nothing, and wishing you had?
- Competition brings out the best in products and the worst in people.
- Treat your password like your toothbrush. Don't let anybody else use it, and get a new one every six months.
- A race horse that consistently..runs just 1 second faster.. than others is worth millions of dollars more...
- Everyone smiles in the same language.
- The moment you flip a coin, you know what your decision is. not because of the side it landed, but because in the few seconds the coin was in the air, you knew what you wanted.
- Go for someone who is not only proud to have you but will also take every risk and chance just to be with you.
- Pessimists see pollution and smoke..optimists see the thrill , bonhomie, and buoyant celebration in a bonfire.
- Live. love. learn. and leave a legacy.
- Whatever you do will be insignificant, but it is very important that you do it".
- Sometimes forgiveness is the only solution to a problem...
- Love is needing someone. Love is putting up with someone's bad qualities because they somehow complete you.
- Better a friendly refusal than an unwilling consent.

Brain Teasers

Identify the following arrow marked RBC pathologies / types.

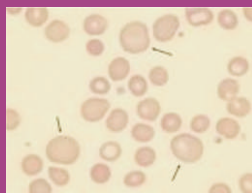
1



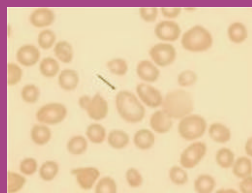
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3



4



Answers: 1. Stomatocyte 2. Pappenheimer body 3. Macrocyte 4. Macro-ovalocyte.

INTERPRETATION

AMINOACIDURIAS AND INBORN ERRORS OF METABOLISM

AMINOACIDURIAS - ITS THREE TYPES: Aminoaciduria means that there is an excess of amino acids in the urine. There are three type of aminoacidurias: **Overflow:** The plasma levels of amino acids are increased and results in more amino acids being filtered at the glomeruli. This excess in amino acids exceed the threshold rate and increased amounts of amino acids are excreted in the urine. **No-threshold:** This involves those amino acids that are not normally recovered by the tubules. When there is an increase in the plasma concentration there will be a corresponding increase of these amino acids in the urine. **Renal aminoacidurias:** These are due to a primary metabolic disorder as phenylketonuria, cystinosis, and 5-hydroxyindoleacetic acid. Secondary disorders are where amino acids are spilled into the urine because of an existing problem such as a severe liver disease (hepatitis) or a generalized tubular disorder resultant of an existing disease as Fanconi's syndrome.

FOUR DISORDERS THAT INVOLVE THE RENAL SYSTEM THROUGH DEFECTIVE TUBULAR REABSORPTION MECHANISMS: **Fanconi's syndrome:**

A congenital hypoplastic anemia with a fatal prognosis, death occurring before puberty. It is characterized by aminoaciduria, glycosuria, phosphaturia, bicarbonaturia, uricaciduria. Bence Jones proteinuria can be frequently found in these patients. A patient who presents with this disorder could also have been previously diagnosed with cystinosis, multiple myeloma, Wilson's disease, Amyloidosis, heavy metal poisoning, or Lowe's syndrome. If a previous diagnosis is the case, then Fanconi's syndrome is acquired. **Cystinosis:** An inborn error of metabolism which may be benign or fatal. Cystinosis is characterized by the deposition of cystine in the lysosomes of all the cells. When cystine deposits in the tubular cells, there is a loss in the ability to reabsorb a number of metabolites or to acidify urine. Glucosuria, polyuria, aminoaciduria, phosphoruria, and other urinary anomalies result. It can progress to renal failure. **Wilson's disease:** An autosomal recessive disease characterized by cirrhosis of the liver, splenomegaly, degenerative changes in the brain, accumulation of copper in the renal cortex, decrease in tubular function, proteinuria, aminoaciduria, phosphaturia, hypercalciuria, glucosuria, and uricaciduria. There is loss of the ability to acidify the urine. It has been found that if the accumulation of copper can be controlled, then renal functions can return to normal.

Galactosemia: A disorder in which galactose cannot be metabolized. There are two types of galactosemia; (1) galactose-1-phosphate uridyl transferase deficiency and (2) galactokinase deficiency. Galactose-1-phosphate uridyl transferase deficiency galactosemia is the classic form and most serious. Untreated infants will survive only a few weeks, rarely a few months. Clinical findings include jaundice, hepatosplenomegaly, cataracts, hemolytic anemia, proteinuria, aminoaciduria, and galactosuria. This condition can be detected by screening for the presence of a reducing sugar in urine with the clintest tablet when the glucose oxidase test is negative. Diet restrictions prevent the disease.

PHENYLKETONUIRA AND HOW TO SCREEN FOR ITS PRESENCE:

Phenylketonuria (PKU) is the best known of the aminoaciduria's. It is due to a deficiency of the enzyme "phenylalanine hydroxylase", which when present converts phenylalanine to tyrosine. PKU causes other amino acids to appear in urine in abnormal amounts, inhibition of the transport of tyrosine, and has an inhibitory effect upon the absorption of amino acids across the intestinal wall. PKU is a disorder which must be caught early. If left untreated, mental retardation sets in by the third week and the maximal effects are accomplished by the eighth or ninth month. Initial screening for PKU is a blood test and does not require urine. A blood specimen should be collected on the third day to allow the infants metabolism to be stabilized. To collect blood soon (approximately four hours) will identify a number of PKU disorders but

will miss some. A popular and widely used test is the Guthrie test. Once the PKU disorder has been identified, treatment consists of maintaining the child on a phenylalanine free diet until about it for the first decade of its life or longer if medically required. **Screening urine** for PKU does have some value as a follow-up test for: [1] **Follow up** on a questionable diagnosis. (a) Girls are slower to develop diagnostic phenylalanine levels than boys and may escape detection of the disorder with an early blood test. (b) Late detection with treatment can prevent further mental retardation. [2] **Monitor diet** to see if the patient is "cheating". [3] **Monitoring** the dietary intake of pregnant PKU females. If a pregnant PKU woman allows her phenylalanine levels to escalate, it will have a detrimental effect upon the developing fetal brain. **The urine** of a PKU patient contains phenylpyruvic acid which give it a mousy or barnyard-like odor. The 10% ferric chloride test is a quick screening method to detect the presence of PKU. A positive test is indicated by a transient, transparent blue to blue-green color.

THE FERRIC CHLORIDE TEST- ADVANTAGES AND DISADVANTAGES:

The ferric chloride test is a non-specific test and will react with any chemical that will form complex with the ferric ion. Its advantage lies in the ease in which the test can be performed and its disadvantage is due to its non-specificity.

THE GUTHRIE TEST: This is a bacterial inhibition test that depends upon the germination of spores of *Bacillus subtilis* enhanced by the presence of phenylalanine. A culture plate containing an inhibitor in the agar is plated with the spores. Separate paper disks containing the patient's blood, a standard amount of phenylalanine, and without phenylalanine; are placed on the plate and incubated. If growth occurs around the patient's disk and that of the phenylalanine standard, then the test is positive for PKU. No growth will occur around the negative control disk. The Guthrie test is a reasonably accurate test.

NEWBORN SCREENING FOR INHERITED DISORDERS: Ideally all newborns should be screened for inherited disorders. At least the following eleven diseases should be screened for e [1] phenylketonuria (PKU), [2] hypothyroidism, [3] galactosemia, [4] hemoglobinopathy, [5] maple-syrup urine disease, [6] homocystinuria, [7] biotinidase deficiency, [6] adrenal hyperplasia, [9] tyrosinemia, [10] cystic fibrosis, and [11] toxoplasmosis. At the very least PKU and hypothyroidism testing must be done for all newborns. Galactosemia and haemoglobinopathies must also be routinely tested for.

IMPORTANCE OF URIC ACID IN URINE TESTING: Uric acid is an end product of nucleoprotein metabolism. The amount that appears in urine is dependent upon the amount of endogenous and exogenous purines metabolized. Uric acid will be excreted in the urine as uric acid crystals, as a solute, and as sodium, potassium, or ammonium salts of uric acid (urates). The average mixed diet will produce from 0.5 to 1.0 grams of uric acid in a 24 hour urine specimen. In renal disorders, uric acid values in urine does not fluctuate, therefore this data is not clinically significant. Urine testing for uric acid is simply not done. Urine values for uric acid will increase in polycythemia vera, leukemia, cytotoxic drug medication, liver disease, and febrile illness.

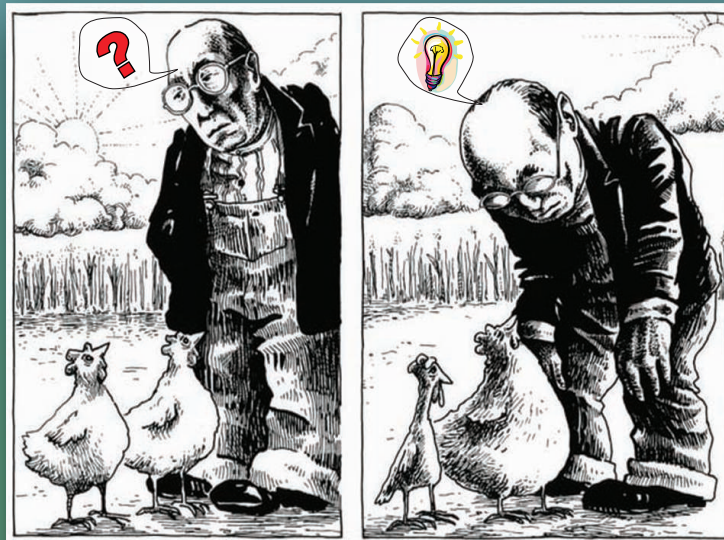
HOMOCYSTEINURIA AND HOW TO SCREEN FOR THIS DISORDER:

Homocystinuria is a biochemical abnormality due to a homozygous, autosomal recessive trait, not a specific disease. There are several variants of this abnormality, but the most common is due to a deficiency in the enzyme "cystathionine β -synthase. Many patients will die from thromboembolic problems. Clinical manifestations are ectopia lentis, osteoporosis, scoliosis, and sometimes kyphosis, and mental retardation in a significant number of patients. Normally, homocysteine is not detected in plasma, but in this disorder it is readily detected in urine. The urinary cyanide-nitroprusside or silver-nitroprusside test is positive (red-purple color). Fresh urine is recommended for testing and if the urinary tests are positive, they should be followed up with more specific/sensitive spectrophotometric procedures. Urine with this chemical may have a sulfur-like odor.

(To be continued)

DIFFERENTIATION

Between possible
Prostate Cancer
and BPH?



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10 Test

CANCHECK-PSA

CHEMILUMINESCENCE
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Rapid test for PSA in serum / plasma / whole blood

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