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Contents

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Microarray Technology in Biomedical Research

T. Samuel Shomaker MD, JD and Kenneth Ward MD

T. Samuel Shomaker MD, JD

Abstract

Microarrays have dozens to millions of probes attached to an inert surface allowing high-throughput analyses of many biologic processes to be performed simultaneously on the same sample. Microarrays with nucleic acid probes are now widely used for gene expression analysis, DNA re-sequencing, single nucleotide polymorphism genotyping, and comparative genomic hybridization. This technology is accelerating research in many fields and now microarrays are moving into clinical application. This review discusses how the microarray facility at the new Kaka'ako campus of the John A. Burns School of Medicine will impact molecular diagnostics, pathogen detection, oncology, and pharmacogenomics.

Introduction

Medical science continues to advance through incorporation of new developments in nanotechnology, informatics, molecular biology, and many other disciplines. Since the mid-1970s, recombinant DNA methods, automated DNA sequencing, the polymerase chain reaction (PCR), and other breakthroughs have revolutionized biomedical research. Microarray analysis is one of the newest tools available to biomedical investigators. The new Kaka`ako campus of the John A. Burns School of Medicine (JABSOM), University of Hawai`i contains research facilities designed to enhance JABSOM's ability to compete for extramural grant funding. The Biomedical Sciences Building will make available to JABSOM faculty the latest in scientific equipment, including microarray technology for nucleic acid analysis. This review will focus common research and emerging clinical applications of DNA microarrays.

Microarray chips are flat, two-dimensional wafers made of plastic, glass, nylon, or silicon that have dozens to millions of molecules (oligonucleotides, cloned DNA, antibodies, or peptides) placed at precise locations distributed across the surface. These attached molecules are used as probes to study a variety of biological phenomena simultaneously in a test sample. Manufacturers can reliably place picogram amounts of probe at each location by spacing them just a few micrometers apart. The identity of the molecule fixed to each spot for any particular array design never changes. The microscopic scale of the array allows high-throughput "parallel" testing. Fodor et al launched the microarray era in 1991,[1] borrowing techniques from computer chip manufacturing that allowed parallel synthesis of a large number of oligonucleotide probes on silicon wafers. Hybridization – the ability of two complementary molecules to lock together – is the central design element for microarray assays. For instance, DNA microarrays depend upon the fact that single-stranded DNA probes will hybridize or "stick" to the strands of DNA sample to be tested following the usual rules of base pairing (A to T, C to G). Complementary DNA sequences have incredibly high affinity for each other and the target DNA in a solution literally "finds" and attaches itself to the immobilized probe DNA. Probes as short as 20 nucleotides in length can be highly specific; even a single mismatched base greatly reduces the strength and likelihood of hybridization. Longer probes will usually allow greater sensitivity. Probes are usually prepared either by chemical synthesis or by using the polymerase chain reaction (PCR). Other types of microarrays, such as arrays that use antibodies to probe for antigens or proteins to probe for protein interactions (see Table 1) also depend upon the chemical and physical forces attracting complementary molecules.

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Table 1.— Other Types of Microarrays

Antibody Microarrays	Antibodies are arrayed and used to study protein levels.[45]
Carbohydrate Microarrays	These arrays rapidly screen protein binding to carbohydrates.
Cell Arrays	Living cells are placed at defined locations on chips and then tested for a variety of reactions to applied agents.
Chemical Microarrays	Chemical libraries of potential drugs are bonded to the array and protein affinities to these molecules are tested.
Protein Microarrays	These chips are designed to measure changes in protein expression, protein - protein interactions, and the proteomic response to drugs and other stimuli.
Tissue Microarrays	Tissue microarrays allow the simultaneous analysis of multiple samples of a tissue or cell line arranged in an array format to allow high-throughput molecular profiling of the tissue.

Most microarrays use fluorescent tags as the means of identifying whether hybridization has occurred. Computerized array scanners can rapidly detect very low levels of fluorescence and map the signal to its location on the array with great certainty. The signal is captured by a high-resolution "digital" camera.

The upfront cost of microarray instrumentation is high. Furthermore, most chips cost several hundred dollars each and can only be used once. Fortunately as manufacturers increase their sales and as competing products emerge, array prices are coming down. On a "per test" basis, microarrays offer relatively inexpensive, rapid, and simple testing compared with other molecular methods. "Homemade" microarrays can be produced using inexpensive spotting devices that work in a manner similar to ink-jet printers accelerating the pace of biomedical discoveries.

Methods

Research Applications

DNA Re-Sequencing Chips: DNA microarrays can be used to rapidly and accurately sequence known genes. For any specific base pair in the human genome, a series of oligonucleotide probes can be constructed that either perfectly matches the normal sequence or variant sequences. Redundant probes would be spread over different geographic areas of the microarray chip, lessening the potential for contamination from air bubbles or extraneous debris.

Comparative Genomic Hybridization/DNA Copy Number: In comparative genomic hybridization (CGH), DNA to be tested is labeled with one fluorescent dye and added in equal amounts directly to normal reference DNA labeled with a second dye. This mixed sample is then hybridized to DNA microarrays with probes from every region of the genome. Fluorescence ratios for every probe spotted on the array are calculated. If any area of the genome is duplicated (as with trisomy) the test sample will show an abnormally high signal for probes matching the duplicated region. If any areas are missing (as with a microdeletion) then the test sample will show abnormally low signal in the affected regions. Array-based CGH can perform "molecular karyotyping"[2] leading to more rapid and accurate diagnosis of micro deletion syndromes than conventional cytogenetic techniques.

Expression Profiling: Genes don't result in clinical phenotypes unless they are expressed as messenger RNAs first and, ultimately, as proteins. DNA microarrays are used widely to study mRNA.[3] Because RNA is inherently unstable, mRNA is extracted from fresh cells or tissues to be studied and then reverse transcribed into a stable cDNA copy. Label is incorporated into the cDNA molecule as it is synthesized and then the cDNA is placed on the array. DNA probes are now available for cDNA for every known and predicted human gene, and also for the genomes of all common experimental organisms. These probes are arrayed as uniform sets, and the pattern obtained when the labeled test sample hybridizes to the array is the gene expression profile or signature for that test material. There are probe sets that can examine every gene simultaneously or chips can be designed to focus on particular pathways (i.e. apoptosis).

Differential Expression: Usually cDNA arrays are used to screen for genes that are differentially expressed between two tissues (normal and diseased, treated and untreated). Expression analyses often consider what the genes are doing over time or after an intervention.[4] For example, by comparing the genes expressed in both normal and diseased ovaries, it might be possible to identify the genes, proteins, and pathways that are part of that disease process, leading to the discovery of new biomarkers predicting clinical outcomes. Eventually, drugs may be discovered or developed targeted against these disease pathways. Expression profiles from tens-of-thousands of "reference" experiments are already available and can accelerate the analysis of any new data. Large databases store the expression data and move them between software packages.

Genotyping, Gene Mapping/Discovery: Most diseases have an intrinsic genetic component. The mutations underlying common diseases usually cause minor changes in gene expression or in the amino acid structure of the encoded proteins. For most variant alleles, the effect on the disease phenotype is weak and mutations interact with nutritional, environmental, and other factors before resulting in the disease phenotype. Despite these challenges, microarrays that scan the entire genome in a single experiment have resulted in the discovery of dozens of important disease genes. The most powerful genome-wide approach uses single nucleotide polymorphisms (SNPs): DNA sequence variations that occur when a single nucleotide in the genomic sequence is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome. For single base changes to be considered a "polymorphism" and thus a SNP, the change must occur in at least 1% of the population.

For instance, the Affymetrix HuSNP arrays have either 100,000 or 500,000 single nucleotide polymorphisms (SNPs) selected based on their location, their heterozygosity, and the likelihood that they are genetically linked to each other.[5] These microarrays are used to perform case-control association studies or relative pair studies. Cases and controls are matched for the most readily apparent confounding factors (age, sex, known risk factors, etc.).[6,7] Disease associated alleles with modest relative risks (relative risk of 2 or more) can be detected with manageable sample sizes.[8,9]

Because over 500,000 case control association studies are being tested simultaneously, corrections for multiple testing and very stringent significance levels are used when analyzing results. False positive association studies can occur when ethnicity in the cases and controls are not well matched or if there is hidden population stratification in the cases. Various statistical methods are being developed to deal with this issue[10,11] but ultimately replication in additional independent samples is the best way to be certain of the findings.

Results

Clinical Applications

Disease Diagnosis/Prognosis: As the relationships of individual genes and polymorphism to disease are discovered, this knowledge can be used to develop microarray-based diagnostic and prognostic tests. In 2004, the Food and Drug Administration (FDA) approved the first laboratory test using a microarray for medical use. The

AmpliChip Cytochrome P450 Genotyping Test (Roche Molecular Systems Inc. Pleasanton, Calif.) analyzes two important cytochrome P450 genes. The test detects polymorphisms that interfere with the encoding of liver enzymes that metabolize one fifth of commonly prescribed drugs, thus altering the clinical effectiveness of these drugs.

In the coming decade, microarrays will allow rapid assessment of the fetal genotype in prenatal diagnosis, more accurate and extensive newborn screening,[12] better measures of viral loads and resistance or virulence factors, and more complete characterization of malignant lesions. Bioterrorism concerns and newly emerging epidemics like SARS have already caused development of microarrays for the rapid identification of infected individuals and rapid characterization of the threatening organism.[13] In industrial scale diagnostics, microarrays may be used to detect genetically modified organisms or microbial contaminants in foods.[13] Systems have already been designed to allow "point-of-care" testing by staff with no molecular biology training.

Oncology Applications: All cancers have genetic changes – microarray technology will be useful in assessing the degree of genetic damage in both the primary tumor and the surrounding tissues, which could alert to the probability of tumor recurrence.[14,15] Even though tissue margins close to resected tumors may look microscopically normal, microarrays can detect genetic damage that crosses these histologic margins. Eventually many tumors will be routinely analyzed by microarray technology to predict their sensitivity to radiation and various chemotherapeutic agents, allowing correct selection of primary and adjuvant treatment. Microarrays may be useful in predicting which dysplastic or atypical benign lesions will undergo malignant transformation.[16] Expression profiles of melanoma[17] and breast cancers[17-21] have already led to advances in methods of staging and classifying these diseases. Patients with tumors can be subdivided into distinct groups based on their gene expression profiles, even though there were no obvious pathological differences between their tumors.[22]

Pharmacogenomics/Toxicogenomics: The field of pharmacogenomics is using microarrays to find correlations between therapeutic responses to drugs and the genetic profiles of patients.[23-26] A related field, toxicogenomics, seeks to find correlations between toxic responses to chemicals and changes in the genetic profiles of subjects exposed to those chemicals.[27-29] By identifying individuals with similar biological patterns, microarray analysis can assist drug companies in choosing the most appropriate candidates for clinical trials of new drugs. In the future, this technology may lead to "personalized medicine" in which patients are prescribed drugs that are very likely to be effective and free of side effects given their individual profile.

Pathogen Detection:[30] Diagnostic assays for acute infections are rapidly changing from antibody detection to pathogen detection, from slower culture-based methods to rapid molecular methods, from clinical laboratory based to point-of-care based tests, and from detection of a few organisms at a time to simultaneous detection of multiple pathogens. Microarrays have the ability to detect viruses, bacteria, and other microorganisms all on the same chip. Host studies are unraveling the development and activation of both innate and adaptive immunity; others are studying global gene expression of both the pathogen and the patient during progression. In the near future, virulence factors, resistance factors, and host response to the pathogen will all be monitored in parallel.[31,32]

Sequence based tracking of pathogens has allowed more thorough evaluation of recent outbreaks such as monkey-pox or SARS. Rapid point-of-care (POC) devices allow detection and surveillance of infections at ports of entry and will be very helpful in the event of a bioterrorism attack.

Problems and Pitfalls: Despite their promise, microarrays are still too costly and present too many technical challenges for widespread clinical use. However, greater automation and increasing sophistication of analytic paradigms are already on the horizon and the cost of arrays will decrease as patent protections expire.

As microarrays have improved, data analysis rather than data production has become the critical issue.[33-42] With so many features being tested at once, corrections for multiple testing need to be applied to any tests of significance. Unfortunately, low-level signals can be missed because of the need for conservative statistical analyses. Interpretation of gene expression has more pitfalls than interpretation of genotyping or re-sequencing chips,[3, 43] primarily due to the unstable nature of mRNA. Rigorous quality control is essential.

Sophisticated software is used to detect genes with different expression under different conditions. Expression "constellations" can involve hundreds of individual genes. Three dimensional scatter plots are used to determine whether related specimens cluster together. This type of clustering analysis can give clues to previously unrecognized pathways.

Analysis of microarray outputs can build upon known relationships between genes registered in public databases. For example, the National Center for Biotechnology Information, part of the National Library of Medicine, hosts the Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo) as a public repository of gene expression data. This database already contains over a half a billion individual gene expression measurements. A lack of standardization makes it difficult to compare data produced by different systems and has made it difficult to merge data.[44]

Discussion

By providing global views of molecular processes, microarrays enable systematic surveys of variations in DNA sequence and gene expression. Microarrays are fueling novel and expansive research. The current $2 billion per year market for microarrays in the United States is growing by over 30% each year. Patients are likely to benefit from this research activity as it leads to improved genetic diagnostics, personalized treatments, and more rapid and definitive testing of clinical specimens.

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Correlation and Consistency of Pain Severity Ratings by Teens Using Different Pain Scales

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Abstract

100 teens ranked pain experienced for their most recent "shot" on three different scales: casual 0-10 scale (mean 3.3), faces scale (mean 2.8), and 10 cm visual analog scale (mean 2.4). All pain scores showed wide variation (poor validity). Pain severity values were not equivalent across the different pain scales with the casual 10 scale most likely to overestimate pain values.

Introduction

Pain is a complex and subjective experience that affects each individual differently. It is difficult to objectively measure pain; however, pain research studies have relied upon the use of self-reporting scales to measure pain severity.[1] All hospital departments are now required to document a pain severity assessment on all patients. The faces scale and the 10 cm visual analog scale (VAS) are two scales that are the most commonly used in pain research studies. A 0-10 scale is used commonly in clinical practice, in which patients are asked to rank their pain from 0 to 10. A statement commonly clarifies this scale such as, 0 means there is no pain and 10 means that the pain is very bad. For this report, this type of pain assessment commonly used in clinical practice will be called the casual 10 scale, to distinguish this from the 10 cm VAS, which is explained in more detail and carried out in a more rigorous (less casual) fashion. The six-graded faces pain scale used in this study is one that is often employed in the clinical setting, from patients as young as 3 years old to the elderly. There are six faces ranging from a smiling face to a crying, sad face, with comments below ranging from "no hurt" to "hurts a whole lot".[2] There are some concerns regarding its validity since it does not take into account cultural biases toward pain and that the use of a happy face for the "no hurt" may confuse patients because not being in pain is not the same as being happy. The 10 cm VAS is another commonly used pain scale. It is a scale that requires no verbal or reading skills, versatile enough to be employed in a variety of settings, and it has been shown to be a very reliable measurement of pain.[3] Patients are asked to mark a point on a 10 cm line from 0 (no pain) to 10 (the worst pain imaginable) that correlates with their pain.

It should be noted that some reports refer to a "verbal analog scale" or "verbal analog score" which also abbreviates as VAS. A verbal analog scale is similar to what we are describing as the casual 10 scale. In this report, VAS refers to the 10 cm visual analog scale.

The purpose of this study is to determine if these three scales are equivalent by studying the correlation and consistency of pain severity ratings by adolescents using these three different pain scales. If these scales are equivalent, then study results using one scale can be extrapolated to another scale.

Methods

Volunteer study subjects ages 11-18 were recruited in high school classrooms and a girls' soccer team. Written informed assent was obtained from volunteers and written informed consent was obtained from parents if the study subject was under 18 years old. Selection bias is minimized since recruitment was done for an entire group (for example, the entire class or the entire team) and most of the members of these groups participated.

Each subject was given a data form and was given both verbal and written instructions to complete the form. Aside from demographic information (subject's age and sex), volunteers were asked to recall the last time they were given a "shot". The definition of "shot" was used loosely to include intramuscular injections, tuberculin (TB) intradermal skin tests, venipuncture, or infiltrated local anesthesia. They were asked what type of "shot" they last received and how long ago they received the "shot".

The subjects were then asked to rate the pain of the "shot" on three different pain scales. The first, the casual 10 scale, asked subjects to rate their pain from 0-10, where 0 is no pain and 10 is a lot of pain. The second scale, the faces scale asked subjects to rate the pain of the same shot by circling the face and corresponding description. Since there were 6 faces, each face was given a numerical value (0, 2, 4, 6, 8, and 10) during the data analysis in order to statistically compare this scale with the casual 10 and the VAS. However, these numerical values were not displayed next to the faces,

Table 1.— Pain scale results			
	Casual 10	**Faces**	**10 cm VAS**
– Overall			
Mean	3.3	2.8	2.4
Median	3	2	2
Range	0-9	0-8	0-10
Standard deviation	2.4	2.1	2.0
95% Confidence interval of the mean	2.8-3.8	2.4-3.2	2.0-2.8
– Males			
Mean	2.8	2.4	2.2
Median	2.5	2.1	2.3
– Females			
Mean	3.6	3.1	2.6
Median	2.4	2.0	1.9

Table 2.— Statistical comparisons between scales		
	Means	**p-value***
Casual 10 vs. Faces	3.3 vs. 2.8	0.0004
Casual 10 vs. 10 cm VAS	3.3 vs. 2.4	<0.0001
Faces vs. 10 cm VAS	2.8 vs. 2.4	0.0214

*paired t-test

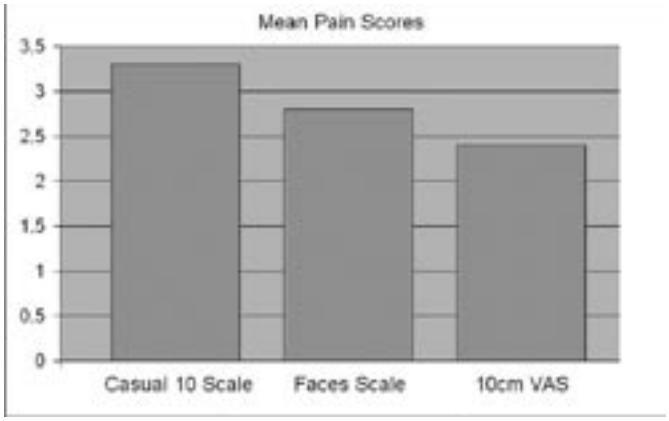

Figure 1.— Mean pain scores

to avoid the numerical similarity from influencing their choice. The final scale, the 10 cm visual analog scale, asked subjects to rate the pain of their shot by placing an X on a 10 cm line marked at 1 cm increments from 0-10 where 0 is no pain and 10 is the most excruciating pain imaginable, comparable to the pain of falling off of a multistory building and breaking multiple bones. Care was taken to ensure that the verbal instructions were kept as consistent as possible for each test group.

Results

Results are summarized in Tables 1, 2, and Figure 1, one hundred volunteers were recruited with a mean age of 15.8 years. There were 60 girls (mean age 15.3) and 40 boys (mean age 16.6). The boys were significantly older than girls ($p<0.001$, t-test). This was skewed by the girls soccer team. Thirteen subjects received flu shots, 13 tetanus toxoid boosters, 38 TB tests, 19 subjects were "not sure," and 17 received "other" shots (specifically two varicella vaccines, one IV, three "novacaine" or similar numbing agents, one hepatitis B vaccine, two allergy injections, one venipuncture, and the other seven were left blank). 17 volunteers recalled that their last shot was less than 1 month ago, 17 were 1-3 months prior, 38 had a shot 4-12 months ago, 26 had shots more than 12 months ago, and 2 were left blank.

Mean pain scores for males and females were not significantly different. Mean pain scores for the younger age group compared to the older age group were not significantly different.

The casual 10 scale ratings resulted in significantly higher numerical values than both the faces and the 10 cm VAS. Comparing the casual 10 and the faces scale, 29 gave identical values and 71 gave different values, of which 49 gave higher values for the casual 10 scale and 22 gave lower values. Comparing the casual 10 scale and the 10 cm VAS, 43 gave identical values and 57 gave different values, of which 50 gave higher values for the casual 10 scale and 7 gave lower values. Comparing the faces scale with the 10 cm VAS, 23 gave identical values and 77 gave different values, of which 49 gave higher values for the faces scale and 28 gave lower values.

Discussion

Pain rating using the casual 10 scale was found to be significantly different than the faces scale and the 10 cm VAS. The higher values suggest that using the casual 10 pain rating will tend to overestimate pain values especially when compared with the 10 cm VAS. The reason for this might just be the casual nature of how the casual 10 scale is administered. In clinical practice, a 0-10 value is obtained in conjunction with other clinical information; history, allergies, medications, vital signs, domestic violence screening, etc. The pain score is just one aspect of the full assessment. Clinicians often comment that the patient says that his/her pain level is an 8, 9, or 10, but he/she looks happy and is reading a book or playing a video game. Compare the casual 10 scale to the 10 cm VAS, which is administered as part of a research study. The accuracy of the pain assessment is the focus of the study, hence a great deal of time is invested in obtaining an accurate pain severity measurement. If a concrete example of a "10" level of pain is given as part of the pain severity assessment, such as childbirth or renal colic, the pain currently experienced can be more thoughtfully assessed. Since adolescents and most males have not experienced childbirth or renal colic, other examples might be necessary to form a perspective. We chose to use "the pain of falling off of a multistory building and breaking multiple bones." It would be difficult for most clinicians to routinely spend this much time on each pain assessment performed.

Another reason might be the description of the casual 10 scale. Considering that a 10 on the casual 10 scale is commonly described as "a lot of pain" or "really bad pain" as opposed to a 10 on the 10 cm VAS which is "the most excruciating pain imaginable," it would be reasonable to expect that a patient would rate their pain lower on the 10 cm VAS, and higher on the casual 10 scale. However, this again relates to the time spent on obtaining the pain assessment since a clearer definition of "really bad pain," "a lot of pain," or "the most excruciating pain imaginable," all require time for the patient to properly reflect on the appropriate numerical value for his/her pain. One could call this a "bias" but it is really an inherent difference in the two pain scoring methods. In clinical practice, it is unreasonable to assume that clinicians spend the same amount of time in their brief pain assessments compared to pain researchers using a 10 cm VAS. Additionally, for a given patient, different clinicians may obtain pain assessments at different times during the patient's medical encounter. The pain assessment question might be asked slightly differently each time depending on the clinician and how much time is available.

The difference between the faces scale and the 10 cm VAS was significantly different, but the magnitude of the difference was less than the difference between the casual 10 scale and the 10 cm VAS. The faces scale has been shown to be useful in assessing pain ratings in children as well as adults who have difficulty conceptualizing a numerical rating scale for pain and this is a preferred scale for young children.[4] Because of this, the faces scales will likely to continue to be a valuable tool for years to come. Similarly, the casual 10 scale will continue to be used in clinical practice. Therefore it is important that we know that the numerical values of the pain ratings from these three scales are different.

Men and women were studied separately to see if gender was an influencing factor. Adult studies usually show women reporting lower threshold and tolerance for pain and lower pain ratings than men.[5] This relationship was not found in this study. Perhaps in teens who have a more limited pain experience than adults, this gender difference does not yet exist.

There may also be some validity concerns using adolescents as study subjects. Most adolescents are naïve and inexperienced with regard to pain, in that most adolescents have experienced only mild pain in their lifetimes. This may cause an exaggeration in pain levels (they might assign higher numerical values to their pain) compared to adults who have a broader pain experience. Previous studies have found that pain ratings in children tend to decrease as ages increase.[6] The results of our study are limited to the specific age group of the subjects of this study.

Pain assessment and treatment are important aspects of patient care that are often overlooked and/or undertreated.[7] In the past decade numerous health care organizations such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) have stressed the importance of pain assessment and treatment and are now improving current standards of care by requiring health care staff to assess and document pain in all patients by way of pain scales.[8] Pain assessments are required by the JCAHO and charts are routinely audited for pain assessments during JCAHO accreditation reviews. With pain assessments going from being underutilized to required, this suggests that a lot more pain assessments are being done currently than in the past. In requiring a pain assessment on all patients, this has perhaps diluted their true potential benefit since clearly, pain is a more important issue for some patients than others. This has perhaps promoted the casual nature of the casual 10 score. What is currently being done is not the same as the 10 cm VAS. If this was their original intent, a score that is comparable to the 10 cm VAS is not being done in routine clinical pain assessments. The next logical step would be to create a standardized method of pain assessment, applicable to clinical care. It would be difficult to truly employ the rigors of the 10 cm VAS for routine clinical use and a picture scale (such as the faces scale) or an observational scale (such as the face-legs-activity-cry-consolability; FLACC scale) will always be necessary for young children. Ideally, a standardized 0-10 scale using a brief standarized question would reduce the inter-rater variance of clinical pain assessments. This will not necessarily be equivalent to the 10 cm VAS, but at least it would be more reproducible (reliable).

Reliability of the pain score relates closely to its reproducibility, but this does not necessarily make the score a valid one. In other words, for a score to be valid, it must accurately measure the level of pain. For a similarly perceived painful experience, many different patients will report the same numerical score if the pain score is valid. The study subjects in this study all rated painful events that should be roughly similar, yet the wide range of pain scores and the large variance about the mean indicate that: the pain perception of similar procedures is wide-ranging, pain scoring is not valid (as evidenced by the wide ranges), or a combination of these two factors. Many studies have documented system wide failures to treat pain, but the "pain" is measured by these scoring systems which have poor validity. As clinicians, we have all seen many patients who state that their pain number value is high, but they appear to be perfectly comfortable. It would be a poor therapeutic decision to administer a potent analgesic to treat a number that is not a truly valid measure of the patient's pain.

In conclusion, this study has shown that conclusions drawn from pain studies using the 10 cm VAS and faces scales cannot necessarily be applied to values drawn from the casual 10 scale which is the most common pain scale used in clinical practice. This study adds to the body of knowledge that our ability to accurately measure pain is poor, yet we are still reliant upon these scores which are not valid.

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Evaluation of Cryptococcus laurentii Meningitis in a Patient with HIV Infection: A Case Report and Review of the Literature

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Abstract

Cryptococcus neoformans *is the most common cryptococci causing infection in humans. Non-*neoformans *cryptococci have generally been regarded as saprophytes and rarely reported as human pathogens. We report a probable case of* Cryptococcus laurentii *meningitis in a HIV-infected patient and reviewed the literature on risk factors and treatment of this infection in humans. This patient was successfully treated with amphotericin B followed by fluconazole. Awareness of the emerging antifungal-resistant* C. laurentii *strains, as reported in the literature, should be emphasized, especially in immunocompromised patients.*

Introduction

Cryptococcus spp. other than *Cryptococcus neoformans* have generally been considered nonpathogenic to humans. In the United States, the annual incidence of cryptococcosis among HIV-infected patients ranged from 1.6 to 7 cases per 1000 persons and ranged from 0.4 to 5 cases per million non HIV-infected individuals.[1] The majority of the cases were infected with *C. neoformans*, in particular, *C. neoformans* var. *grubii* (serotype A), which accounted for 75-93% of infection depending on geographic regions.[2,3] In contrast, there were fewer than 40 reported cases of non-neoformans cryptococcosis worldwide.[4] Although rare, cases of *Cryptococcus laurentii* infection have been reported in both HIV-infected and non-HIV-infected patients.[5-10] We report a probable case of *C. laurentii* meningitis in a patient with HIV infection and review the relevant literature on *C. laurentii* infection in humans.

Case Report

A 35-year-old Thai man previously diagnosed with HIV infection (CD4 count 12 cells/mm^3 and HIV RNA >10^5 copies/ml) 8 months prior to admission presented to our hospital with a two-week history of high grade fever, progressive headache and vomiting. He had no prior use of antiretroviral (ARV) therapy or opportunistic infection prophylaxis. Upon admission, the physical examination was remarkable for temperature 38.6°C, blood pressure 120/80 mmHg, heart rate 86/min, respiratory rate 20/min, oral thrush and nuchal rigidity. Laboratory data revealed a white blood cell count of 4,100 cells/mm^3 (82% neutrophils, 9% lymphocytes, and 9% monocytes), hemoglobin level of 13.5 g/dl [normal reference; 13-15 g/dl], platelet count of 136,000 cells/mm^3 [normal reference; 150,000-400,000 cells/mm^3] and normal urinalysis, liver function tests, chest radiograph and head computed tomography (CT). The opening pressure for the lumbar puncture was 27 cmH_2O and closing pressure 16 cmH_2O [normal reference; 8-18 cmH_2O]. Cerebrospinal fluid (CSF) was colorless with 50 white blood cells/mm^3 (26% neutrophils, 74% monocytes), protein 203 mg/dl [normal reference; 15-45 mg/dl] and glucose 15 mg/dl (blood glucose 100 mg/dl). India ink staining revealed multiple round to oval, budding, encapsulated yeast cells without pseudo or true hyphae. Cryptococcal meningitis was preliminarily diagnosed and amphotericin B (0.8 mg/kg/day) was initiated. Daily large-volume lumbar puncture was performed to relieve high intracranial pressure (ICP), and CSF was sent for culture. Two blood samples were obtained for culture using the BacT/Alert system (bioMérieux, Inc., Durham, NC) and opportunistic infection prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX, 160 mg of TMP/day) and azithromycin (1,200 mg once weekly) was begun. On hospital day 4, fever subsided and headache and vomiting resolved. All blood and CSF cultures subsequently grew numerous creamy white, round, mucoid colonies with smooth and glossy surface, consistent with *Cryptococcus* spp. This isolate was unable to ferment carbohydrates. The ability to assimilate lactose and melibiose, and negativity for caffeic acid test differentiated it from *C. neoformans*. Its ability to grow at 37°C was unusual for non-neoformans cryptococci, but was characteristic for *C. laurentii*. The API 20C Yeast Identification system (bioMérieux Vitek, Inc., Hazelwood, MO), that was determined to reliably identify *C. laurentii*,[11] suggested that this isolate was *C. laurentii* with 95% likelihood.

The next most-likely species was *C. albidus* with 20% likelihood. The susceptibility testing based on the Clinical and Laboratory Standards Institute method was unfortunately not performed, because the microorganism was not viable at the time of testing. Since *C. laurentii* was shown to be susceptible to amphotericin in previous case reports[12] and the patient was clinically improved, amphotericin B was continued for 14 days. Blood and CSF culture were later negative on the hospital day 7 and 14. Repeated lumbar punctures revealed an opening pressure of 18 cm H_2O and 14 cm H_2O on day 7 and 14, respectively. After 14 days of treatment, the patient was discharged home with fluconazole (400 mg/day), TMP-SMX (160 mg of TMP/day) and azithromycin (1,200 mg once weekly). GPOvir (stavudine 30 mg, lamivudine 150 mg and nevirapine 200 mg) one tablet every 12 hours was started on two-week follow-up and opportunistic infection prophylaxis medications were all continued. At three-month follow-up, there was no evidence of recurrent or ongoing infection and the dose of fluconazole was changed to 200 mg/day as suppressive therapy.

Discussion

Cryptococcus laurentii is a rare non-neoformans cryptococcus that has been associated with human infections.[5-10] Although the natural habitat and prevalence of *C. laurentii* in the environment has not been clearly established, the incidence of *C. laurentii* isolated from sterile and non-sterile body sites is less than 0.1%.[13] *Cryptococcus laurentii* has also been reported to colonize the oropharynx in a leukemic patient.[14] We report here the probable case of *C. laurentii* meningitis, based on available diagnostic methods, with fungemia in a HIV-infected patient and review relevant literature on this infection.

Two cases of *C. laurentii* meningitis (including our probable case) have been reported in HIV patients (Table 1). Both patients had a CD4 count < 50 cells/mm^3. In non HIV-infected individuals, there were a total of 17 reported cases of *C. laurentii* infection (Table 1). Indwelling of catheter associated devices, prematurity, previous broad-spectrum antibiotic therapy, chronic steroid exposure, intravenous drug use (IVDU), neutropenia, hereditary immunodeficiency disorder and underlying solid and hematologic malignancy are associated risk factors. While all infection episodes in HIV patients were community acquired, most infections in HIV-negative individuals were often associated with nosocomial sources.

Historically, combination therapy with amphotericin B and flucytosine or amphotericin B alone has been reported to control the infections in 90% of *C. neoformans* infection.[15] Our patient and another reported HIV-infected case responded favorably to amphotericin B with or without flucytosine followed by fluconazole.[6] In addition, 11/17 (65%) reported cases of *C. laurentii* infection in HIV-negative patients also responded well to amphotericin B alone or amphotericin B with flucytosine.[4-7,9-10,12,16-19] Together, these data suggest that there was no difference in treatment schemes between infections caused by *C. neoformans* and *C. laurentii*. Although not recommended as the first line therapy in all patients with cryptococcal infection,[20] successful treatment outcomes have also been reported with the use of fluconazole [5 of 17 cases (29%)] in non HIV-infected patients. Removal of catheter devices seemed to play an important role in management of these patients and all of them had mild non-disseminated infection.[4,16,17,21,22] In our literature review, there have been 4 case reports of antifungal resistance in *C. laurentii* infection; all were reported resistant to flucytosine and one was resistant to fluconazole.[4,5,9] This emphasizes the need to be vigilant for the presence or emergence of resistant *C. laurentii* strain to antifungal agents.

Because elevated intracranial pressure (ICP) is a common feature of cryptococcal meningitis and CSF pressure ≥ 25 cm H_2O correlates with high pathogen burden, higher incidence of neuropathies, and decreased survival, reduction of CSF pressure is recommended to provide relief of symptoms and improve outcomes.[15] However, aggressive management of elevated ICP has not been employed consistently in HIV-negative patients with cryptococcal meningitis and its impact on outcomes remains unclear.[20] In our patient, daily large-volume lumbar puncture was performed and was associated with a good clinical response without any neurological complications.

With the increase in use of medical devices, greater number of immunocompromised patients, as well as, advances in chemotherapy and immunosuppressive therapy, there will be an increasing number of emerging fungal infections. The advances in diagnostic technology can definitely diagnose unusual organisms more quickly and accurately. Clinicians should be aware of this serious uncommon infection in immunocompromised patients who are at risk as well as the emergence of antifungal-resistant strains. Additional studies are needed to further characterize the risk factors, treatment and outcomes of *C. laurentii* infection.

See Table 1 next page.

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Table 1.— Clinical features of previously published cases of *Cryptococcus laurentii* infection

Case No.	Age (Year)/Sex	Underlying condition(s)	Risk factor(s)	Clinical presentation	Clinical diagnosis	Specimens (No. of cultures)	Treatment	Out-come	Refer-ences
1	35/M	HIV	CD4 count = 12 cells/μL	Fever, headache, vomiting	Meningitis, Fungemia	CSF (1) Blood (2)	AmB→Flu	Cured	Our Case
2	27 days/M	Prematurity, hypoplastic lungs, bilateral hydronephrosis, posterior urethral valves	CVC, urinary catheter, prior antibiotic exposure	Hypotension, tachycardia	Fungemia	Blood (1)	AmB + flucyto-sine + catheter removal	Cured	4
3	27/F	Bacterial endocarditis, PID	IVDU, PICC	Fever, chills, painful cutaneous nodules	Fungemia	Blood (1)	Flu + catheter removal	Cured	4
4	16/M	Solid tumor	CVC	Fever, hypotension	Fungemia	Blood (1)	AmB + catheter removal	Cured	5
5	57/M	AML	CVC, prior antibiotic exposure, neutropenia, prior steroid exposure	Fever	Fungemia	Blood (2)	AmB + catheter removal	Cured	5
6	40/M	Remote dog bite, mycobacterial skin lesion	Prior antibiotic exposure	Cutaneous granulomatous nodules	Cutaneous infection of left leg	Lesion biopsy (2)	AmB	Cured	6
7	18/F	Intracranial hemorrhage, venous thrombosis	Prior antibiotic exposure, urinary catheter	Fever	Fungemia	Blood (2)	AmB→Flu	Cured	7
8	34/M	AIDS	CD4 count = 9 cells/μL	Fever, anorexia, headache	Meningitis	CSF (1)	AmB + FC→Flu	Cured	8
9	55/F	Adenocarcinoma of right breast, dermatomyositis	Prior steroid use	Asymptomatic right upper lobe cavity lesion (lung)	Lung abscess	Bronchial biopsy (1), sputum (1)	AmB	Cured	9
10	51/M	No	Pathogen exposure at work	Tumor-like plague at back, fever, headache	Cutaneous infection, meningoen-cepahlitis	Skin biopsy (1)	AmB + FC	ND	10
11	Prema-ture/F	Prematurity	PICC, prior antibiotic exposure, parenteral alimentation	Hypothermia, circulatory and respiratory insufficiency	Fungemia	Blood (2)	AmB + catheter removal	Cured	12
12	17/M	Leukemia post BMT	Prior antibiotic exposure, CVC, neutropenia	Fever	Fungemia	Blood (2)	Flu (oral)	Cured	16
13	26/M	Solid tumor	Prior antibiotic exposure, CVC, neutropenia	Fever	Fungemia	Blood (2)	Flu + catheter removal	Cured	17
14	50/M	NHL	CVC, prior antibiotic exposure, neutropenia, prior steroid exposure	Fever	Fungemia	Blood (2)	AmB + catheter removal	Cured	17
15	51/ND	DM, contact lens wearing	No	Central cor-neal ulceration, descemetocele with aqueous leak	Keratitis	Corneal biopsy (1)	AmB + miconazole + enucleation	Cured	18
16	13/F	Chronic kidney disease	Chronic ambulatory peritoneal dialysis, prior antibiotic exposure	Fever, abdominal pain, cloudy dialysate fluid	Peritonitis	Peritoneal fluid (2)	AmB + catheter removal	Cured	19
17	14/F	Chronic kidney disease	Chronic ambulatory peritoneal dialysis, prior antibiotic exposure	Fever, abdominal pain, cloudy dialy-sate fluid	Peritonitis	Peritoneal fluid (2)	Catheter removal + peritoneal lavage with NSS	Cured	19
18	61/F	Chronic uveitis, secondary glaucoma	Prior topical steroid exposure	Deteriorating vision	Endophthal-mitis	Vitreous (1)	Flu (oral)	Cured	21
19	9/M	X-linked hyper-IgM syndrome	No	Headache, nausea, enlarged lymph nodes	Meningitis, lymphadenitis	CSF (1)	Flu	Cured	22

NOTE: Abbreviation: AIDS = Acquired immunodeficiency syndrome; AmB = amphotericin B; AML = Acute myelogenous leukemia; BMT = bone marrow transplantation; CSF = cerebrospinal fluid; CVC = central venous catheter; DM = diabetes mellitus; F = female; FC = flucytosine; Flu = fluconazole; HIV = human immunodeficiency virus; IgM = immunoglobulin M; IVDU = intravenous drug use; M = male; ND = no data; NHL = Non-Hodgkin lymphoma; No. = number; NSS = normal saline solution; PICC = peripheral intravenous central catheterization; PID = pelvic inflammatory disease.

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A case of Enterococcus faecalis prosthetic joint infection: a rare and difficult infection to treat

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Abstract

Enterococcus faecalis septic arthritis in native and prosthetic joints is a very rare infection. A case of an African American man with *Enterococcus faecalis* prosthetic joint infection is presented as well as a brief review of the literature.

Introduction

In the United States, osteoarthritis affects more than 20 million people. Although most osteoarthritis can be managed conservatively, there are a large number of patients who undergo total joint replacement. Approximately 600,000 joint prostheses are implanted annually in the United States.[1] With the advent of new surgical techniques and perioperative prophylatic antibiotic use, prosthetic joint infections for hips and knees have decreased to 0.5-3% and 1-2% respectively.[2] Despite modern medical advances, orthopedic implant surgery infections still occur. Even though such infections are rare, they are extremely difficult to eradicate. Prosthetic joint infections may arise from local spread of periprosthetic infection or via hematogenous seeding. They are often caused by staphylococcal or streptococcal species, although *Enterococcus*, *Pseudomonas*, and anaerobic species are possible. Clinical manifestations are nonspecific and may include fever, chills, swelling, pain, tenderness, or effusion. Elevated ESR, CRP, and WBC count may be seen. Diagnosis is made by the presence of clinical manifestations, intraoperative signs of infection adjacent to the implant, and the growth of pathogens in cultures of surgical specimens. Treatment consists of surgery and antibiotic therapy.[2,3] Presented below is a case of a man with an enterococcal prosthetic joint infection.

Case Presentation

A 64 year old African American man with past medical history significant for obesity, hypertension and osteoarthritis presented to the emergency department in August 2005 with a warm, erythematous, and edematous right knee. He had undergone prosthetic implantation of his right knee in October 2004. That surgery was complicated by coagulase negative *Staphylococcus* and *Acinetobacter* infections. At the time, the patient was successfully treated with arthrotomy, debridement, and antibiotics with retention of components. Approximately one year later, increased pain and swelling of the right knee, chills and subjective fever prompted the patient to seek medical assistance. Pertinent labs revealed a leukocytosis of 11,700/μL and an elevated erythrocyte sedimentation rate of 43 mm/h. Right knee aspirate was obtained (WBC 12,000 cells/mm^3 and 10% bands) and the patient was taken to the operating room for irrigation, removal of the prosthesis, and implantation of an antibiotic spacer. Gross inspection in the operating room revealed severe synovitis and intra-operative frozen tissue demonstrated fibrinous material with greater than 10 PMN's/hpf. Aspirate cultures demonstrated *Enterococcus faecalis* sensitive to penicillin, high concentrations of gentamicin, vancomycin and linezolid. The patient was initially treated with IV ampicillin and gentamicin (no checkerboard testing performed) for four weeks and then received oral linezolid for two weeks to complete his long term antibiotic course (total course of six weeks) at home in Korea. The oral formulation of linezolid was chosen for its activity against our patient's isolate, good oral bioavailability, reported excellent tissue and bone concentrations, and convenience of administration. The patient continued physical therapy for the remainder of his hospital course. After counseling, our patient accepted the potential for hematologic toxicity over the potential toxicities of long-term intravenous catheter placement and administration of frequent IV antibiotics that would have prevented his return to his job in Korea. Upon discharge the patient was instructed to obtain weekly CBCs while on linezolid therapy. He underwent successful reimplantation of a new prosthesis (no culture of joint obtained) six weeks later.

Discussion

Enterococci are emerging as one of the most common causative organisms of prosthetic joint infections after *Staphylococcus aureus*, coagulase-negative staphylococci and streptococci.[2] Raymond *et al*. reported 11 cases of enterococcal prosthetic joint infections in 1995.[3] Three published articles on prosthetic joint infections since then have included *Enterococcus*

species as pathogens.[4, 5, 6] We will briefly discuss the risk factors, pathophysiology, and various therapies for successful treatment of enterococcal prosthetic joint infections.

Prosthetic joint infections can be associated with factors related to the patient, the operating room, surgical techniques, or perioperative care. Since the early 1980's randomized, placebo-controlled trials clearly established the benefit of prophylactic antibiotics in the perioperative period and such strategy is currently standard of care.[2] Risk factors such as obesity, immunosuppression, previous prosthetic joint infection, diabetes mellitus, and increased surgical time are associated with higher infection rates. The pathophysiology of prosthetic bone infections is hypothesized to start with the formation of a biofilm around implantable devices. This biofilm is believed to be the nidus for infection. A layer composed of host-derived adhesions (such as fibrinogen, fibronectin, and collagen) forms on the surface of the implant and allows the adherence of free-floating organisms. The creation of this bio-film provides the medium for which bacterial cell division, cell-cell signaling, and antibiotic resistance can thrive.[7]

Our patient was successfully treated for *Enterococcus faecalis* prosthetic joint infection with two-stage exchange and long interval (six-eight weeks) reimplantation, and long-term antibiotic therapy. Surgical treatment options for prosthetic infections include debridement with retention of the prosthesis, one- or two-stage exchange, resection arthroplasty, arthrodesis, and amputation.[1] In their review of prosthetic enterococcal joint infections, Raymond *et al*. noted that in eight of the nine cases in which the prosthesis was removed early, including four cases in which a two-stage procedure was performed, the patient was clinically cured. Initial treatment with retention of the prosthesis in the remaining two cases, however, were not successful and subsequent removal of the prosthesis was needed.[3] In patients with compromised tissue or difficult to treat microorganisms such as oxacillin–resistant *S. aureus* (MRSA or ORSA), other multidrug resistant bacteria, *Enterococcus* species, and fungi, a two-stage replacement with long interval (six-eight weeks) reimplantation results in better function and higher cure rates.[7]

Conventional treatment for infected prostheses involves long-term, organism specific antibiotics along with appropriate surgical intervention.[4] Specific antibiotic regimens depend on the results of cultures and antimicrobial susceptibility, as well as patient factors that might include allergic reactions and availability of or access to home health care for intravenous infusions. *Enterococcus faecalis* is often susceptible to ampicillin and the synergistic combination of ampicillin (cell-wall agent) and an aminoglycoside can be bactericidal.[8] Therefore, infections caused by penicillin susceptible *Enterococcus* species are often treated initially with intravenous penicillin G or ampicillin plus an aminoglycoside followed by oral amoxicillin to complete the prescribed treatment course. Zimmerli et al. recommended total treatment durations in hip and knee prosthetic joint infections of three and six months respectively. In the event of a two-stage procedure with a long interval reimplantation, antimicrobial therapy can be shortened to six weeks after explantation.[7]

Although successful treatment of a prosthetic joint infection can be achieved in most cases, the outcome of complete eradication of the pathogen may be compromised with the increase in antibiotic resistance.[8] Recently, two published articles addressed such an issue by using linezolid as treatment for resistant organisms. Bassetti *et al*. completed a retrospective evaluation of 20 patients diagnosed with gram positive prosthetic joint infection and treated with intravenous and/or oral linezolid for six-ten weeks. Only one strain of *Enterococcus* species was included and treatment with linezolid was well tolerated. Four patients with staphylococcal infections relapsed at long term follow-up.[5]

Rao *et al*. prospectively monitored 11 nonrandomized patients who received oral linezolid for treatment of osteomyelitis or prosthetic joint infection. They included one patient with an infection caused by vancomycin sensitive *E. faecalis* who was treated for eight weeks, and one patient with vancomycin resistant *E. faecium* infection who was treated for 19 weeks. Both of the patients were treated for osteomyelitis and two year follow-up showed remission of infection. This study concluded that oral linezolid was an attractive alternative for treatment of bone and joint infections but weekly CBCs were recommended to detect hematologic abnormalities.[6]

Although the *Enterococcus faecalis* isolate tested in our patient was sensitive to penicillin, we chose not to transition his intravenous ampicillin/gentamicin to oral amoxicillin. While penicillin or ampicillin/amoxicillin are the antibiotics of choice for treating enterococcal infections such as urinary tract infections, peritonitis and wound infections that do not require bactericidal treatment, most experts recommend that more recalcitrant infections such as endocarditis be treated with a combination of a cell wall-active agent (usually penicillin, ampillicin or vancomycin) with an aminoglycoside.[9] In our opinion, infection of a prosthetic joint was more analogous to endocarditis (where monotherapy with penicillin is plagued with relapse rates of 30-60%) than a wound infection, and thus monotherapy with oral amoxicillin would have been suboptimal. Continued therapy with ampicillin and gentamicin for the entire six week course would have been another treatment option, but was impractical given the patient's desire to return to Korea, and would have risked nephrotoxicity and ototoxicity from prolonged use of gentamicin. Given the rarity of Enterococcal prosthetic joint infections, there are no large scale studies comparing different treatment regimens, and thus physicians are faced with extrapolating data from small case studies. Based on the available data, and recognizing that prolonged use of linezolid can be complicated by cytopenias and neuropathies, we opted to complete this patient's antibiotic course with oral linezolid, and had a successful outcome.

In conclusion, prosthetic joint implantation is now a common procedure that provides patients with improved ability to perform and function. As the demand for such highly sought after procedures grows exponentially, the chance for complications due to infection are much greater. Prosthetic joint infections have proven to be very difficult to fully eradicate even with surgical interventions and long-term antibiotic treatments. Consultation with an infectious disease specialist is recommended for appropriate antibiotic management of infected prosthetic joints. Prevention of prosthetic infection is desirable and it is important to include *Enterococcus faecalis* as a potential cause of such rare infections.

***References** p. 273*

HAWAI'I MEDICAL JOURNAL

Educating Tomorrow's Physicians About Cancer Clinical Trials

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Introduction

Clinical trials are essential to the advancement of medicine, as they provide the evidence for adopting new treatments and for accepting new methods of disease prevention and detection. The rigorous scientific process standard in clinical trials for cancer has made many types of cancer treatable; today's standard cancer treatments were yesterday's clinical trials. Despite the essential contributions of clinical trials to science and medicine, adult participation in cancer clinical trials remains exceedingly low. In Hawai'i, only about 2% of adult cancer patients participate in treatment trials.[1] These low participation rates present an ongoing challenge to the development and validation of new treatments for cancer.[2]

Background

Previous research, initiated from both patients and physicians has identified a number of barriers to participation in clinical trials. Lack of access to trials,[3] lack of knowledge about trials,[4] distrust of medical research,[5] among many others can account for the reasons why patients do not participate in clinical trials. In a recent meta-analysis conducted to examine reasons for low clinical trial participation, over 100 distinct barriers were cited as contributors to patients' failure to participate in trials.[6] While it is clear that a number of barriers are present, recent research has also demonstrated that adults in the United States have generally supportive attitudes about clinical trials and medical research. For example, the 2000 Cancer Clinical Trials Study cited a detailed analysis designed to reflect the full U.S. adult population regarding knowledge, attitudes and willingness to participate in clinical trials. This study found that a substantial proportion of American adults held positive general attitudes towards participation in clinical trials but had a limited understanding of the exact nature of a study. More than 38% of the adults assessed in this study indicated a positive disposition toward participating in a clinical trial. Projected rates of diagnosis, eligibility, and recruitment indicate that substantially more patients were willing to participate than the 3 to 5 percent currently accrued to studies.[2] These national figures are echoed in Hawai'i. A poll conducted in November 2005 in Hawai'i found that 95% of Hawai'i residents believe that clinical research is valuable, and 60% report that they would be likely to participate in a research study.[7]

Studies indicate a lack of support by physicians and other health professionals as a leading barrier toward public clinical trials knowledge and participation.[8] Physician concerns and reservations regarding their role in cancer clinical trials include: the potentially negative impact of the clinical trial on the doctor-patient relationship,[8,9] concerns that patients would perceive a conflict between the doctor's role as a healer and his/her role in research,[10] physician discomfort with completing the informed consent process, discomfort in describing the uncertainty involved in clinical trials participation to patients, and potential loss of autonomy or control of their patients' care while they are in a clinical trial.[8] A critical factor to the lack of adult participation in clinical trials is a lack of awareness about available trials. A large national survey indicated that approximately 85% of adult cancer patients surveyed in the study were unaware that clinical trials were an option for their treatment.[4]

Improving Participation in Cancer Clinical Trials

The identification of specific barriers to participation in clinical trials has resulted in the generation of a number of potential interventions to increase accrual rates. Community-based educational campaigns[5,6,11] and navigator programs that pair indigenous helpers with patients to serve as guides through the diagnosis and treatment process,[3] among other interventions, have been suggested to increase acceptability of clinical trials as a treatment option among cancer patients and the general public. However, comprehensive strategies that incorporate both patient/public interventions as well as interventions targeting health professionals may have the most success in achieving increased trial participation rates. In response to the need for a comprehensive approach to clinical trials awareness among the general public, cancer patients, and health professionals, the National Cancer Institute's Office of Education and Special Initiatives developed the Clinical Trials Education Series (CTES) in 2001. CTES is a comprehensive set of educational resources designed to inform patients, the public, and health professionals about the importance of clinical trials through print publications, videos, and computer-based presentations. These materials are designed to reach a number of target audiences, and are tailored to fit the learning needs of a diverse constituency.

As the National Cancer Institute's primary link to the public the Cancer Information Service (CIS), and its 15 CIS Regions are located across the United States. Some regions have formed local coalitions to guide program efforts, while others have formed focused partnerships to address specific awareness issues for a particular target population. In the CIS Pacific Region, which serves the state of Hawai'i and the U.S. territories in the Pacific, a Clinical Trials Education Coalition was created in 2002 with two primary objectives: 1) to increase awareness about clinical trials among Hawai'i's health professional community, and 2) to increase awareness about clinical trials among the general public and cancer patients across the state. The Coalition's efforts led to the development of a partnership between the CIS office in Hawai'i, located at the Cancer Research Center of Hawai'i, and the University of Hawai'i, John A. Burns School of Medicine (JABSOM).

Educating Medical Students at JABSOM about Cancer Clinical Trials

JABSOM has partnered with the National Cancer Institute's Cancer Information Service (CIS) to develop a plan to introduce this important information into the educational curricula of their first-year medical students. Building on the strengths of JABSOM's Problem-Based Learning (PBL) structure, two PBL cases were adapted to increase awareness and self-efficacy of medical students in understanding clinical trials. One case requires the application of knowledge related to the availability and acceptability of a cancer clinical trial as a treatment option for cancer patients. The second PBL case asks students to consider the impact of clinical trials in the advancement of medicine, and explains how to engage patients who have questions about clinical trials. Each student was provided with a free bound copy of the CTES workbook entitled "Cancer Clinical Trials: The In-Depth Program." This manual provides detailed information about clinical trials that was pertinent to health professionals including information about drug development, interpretation of results, the FDA approval process, evolution of participant protections, referring patients to trials, and managing barriers towards participation. In addition, the manual provides helpful tips to those unfamiliar with clinical trials, including: 1) how to discuss clinical trials as potential treatment or preventive options, and 2) how to locate and refer patients to accessible clinical trials.

Select students are also provided with practical learning opportunities through internships with physicians conducting clinical trials at two sites that conduct cancer research in Hawai'i. This 'shadowing' opportunity provides early clinical experience and serves to further integrate their newly acquired clinical trials knowledge with hands-on interaction with clinical trials participants. By the end of their participation in the practicum, students are expected to be able to: 1) identify specific types of clinical trials including prevention, screening, diagnostic, and supportive care studies, 2) understand the rationale related to incorporating clinical trials into routine medical care, and 3) identify the elements of clinical trials that provide protection for subjects. Educational outcomes for these activities are currently being collected and analyzed. Discussions are in progress about ways to expand these opportunities, reinforce these concepts and further develop these skills throughout the undergraduate and postgraduate educational programs.

Future Directions

Integration of clinical trials information into the curriculum through the use of standardized patients and other similar innovative measures will continue to enhance students' awareness of clinical trials at JABSOM. Subsequent efforts may incorporate clinical trials education for medical residents as well as practicing physicians and other health care providers. By integrating information about clinical trials into early medical school education, students benefit from awareness of the important connection between research and practice. The incorporation of the development of the CTES tools and clinical trials content into medical school curriculum is both logical and straightforward.

Conclusion

Clinical trials contribute greatly to the advancement of science and the practice of medicine. The Clinical Trials Education Coalition and the CIS have been working collaboratively with the University of Hawai'i John A. Burns School of Medicine through a combination of PBL cases, learning resources, and clinical experiences to expand students' knowledge about clinical trials. The goal of these educational interventions is to better prepare future physicians for their vital role in the clinical trials process, and to impact future clinical trial participation rates of adult cancer patients in Hawai'i. This collaborative effort can serve as a model for efforts to increase awareness and improve attitudes about cancer clinical trials among other health professionals and students throughout the state and the Pacific. Clearly, medical schools provide a unique opportunity to positively influence the attitudes and knowledge of future physicians related to clinical trials. It is hoped that this exposure might lead to a greater propensity among these students to encourage patients to participate in clinical trials when they become practicing physicians.

Topic	Item	Students With Low Confidence
Clinical Trials Process	Identify steps in the drug development process.	76.7%
	Name the various types and phases of clinical trials.	74.5%
Clinical Trials Design	Review key components of clinical trial design.	81.9%
	Define key members of the clinical trial research team.	79.6%
	Describe the purpose of randomization, stratification and blinding in clinical trial protocols.	58.5%
	Name ways patients are monitored in clinical trials.	75.5%
Advancing Cancer Care	Describe the influence of clinical trials results on the standard of cancer care.	76.6%
	Describe clinical trials that have led to advances in cancer prevention, detection and treatment.	84.0%
	Discuss the importance of professional referral and patient participation in the research process.	70.2%
Barriers to Clinical Trial Participation	Compare and contrast benefits and risks of participating in cancer clinical trials.	76.6%
	Identify barriers that deter special populations from participating in clinical trials.	65.7%
	Recognize cost and insurance issues related to participation in clinical trials.	79.8%
Conducting, Referring, and Locating Clinical Trials	Describe the types of sponsorship of cancer clinical trials.	78.6%
	Define the role of the National Cancer Institute in conducting clinical trials throughout the United States.	80.9%
	Identify methods of referring patients to clinical trials.	78.7%
	Demonstrate ways of locating clinical trials resources.	77.7%

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Tocopherols and Prostate Cancer

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In men prostate cancer accounts for nearly one-third of all cancers (excluding skin cancer) and approximately 10% of cancer-related deaths,[1] making it the second leading cause of cancer death in American men. The incidence of prostate cancer, like many others, increases exponentially with age [2] and as shown in Figure 1, exhibits a remarkably high degree of variation by race/ethnicity.[2] While racial variation in rates suggests the possibility of a genetic basis for risk, studies of changes in risk associated with migration suggest that environmental agents may play an equally important role.[2] Evidence accumulated from years of research in divergent fields suggests that both genetics and environment and their interactions may be key to understanding the etiology of this disease and offers insight into the prevention and management of this disease. In particular a number of micronutrients in the diet may serve important roles in both preventing and delaying the progression of prostatic cancer. The development of effective public health strategies for reducing mortality and morbidity associated with prostate cancer will require that we incorporate fundamental research findings from basic science into a new paradigm of intervention that encompasses the spectrum of prostate cancer development from the early mutational changes in normal prostate cells, through progression into detectable disease, and the ultimate development of metastatic disease.

Given the evidence for both significant involvement of environmental and genetic factors in the development of prostate cancer and the generally long latency period involved, there is considerable hope that we can effectively modify risk through relatively modest interventional changes in diet and lifestyle without the risk of significant side effects. In particular the use of micronutrients offers intriguing potential for significantly reducing incidence and mortality from prostate cancer. Recent epidemiologic, molecular, and clinical evidence for tocopherols, selenium, carotenoids, and potentially vitamin D suggest that this array of agents may offer an important arsenal in reducing prostate cancer incidence and mortality.

Tocopherols (Vitamin E)

The importance of Vitamin E in human nutrition with respect to reproduction, muscle function, red blood cell maintenance, and immune function has been recognized for nearly a century, yet it has only been in the past decade that we have begun to appreciate subtle differences in chemistry and biology between the various naturally-occurring forms of the tocopherols (Figure 2) that constitute "Vitamin E" and that may have significant impacts on the incidence of aging-related human diseases. On the basis of various short-term animal assays and its predominance in human plasma, α-tocopherol is generally considered to be the most potent in terms of Vitamin E bioactivity among the tocopherols. On the other hand, γ-tocopherol is the predominant tocopherol in the American diet, is preferentially accumulated in cells,[3] functions as a more effective agent in the prevention of nitrogen radical mediated DNA damage,[4,5] and is superior to α-tocopherol in preventing neoplastic transformation of fibroblasts.[6]

Although the only difference between α-tocopherol and γ-tocopherol is the presence or absence of a single methyl group at the C-5 position (Figure 2), there are profound differences in reactivity between these two molecules that apparently translate into a variety of biological effects. In particular γ-tocopherol is more reactive towards nitrogen-based free radicals such as nitrogen dioxide[4,6] or nitrogen electrophiles such as peroxynitrite,[5] which are generated *in vivo* through the enzymatic formation and subsequent oxidation of nitric oxide. Nitric oxide (NO) is a key molecule in blood pressure regulation, inflammation, cell-mediated immune function and various signal transduction pathways. The nitrogen oxidants that are derived from NO are particularly reactive towards DNA and can lead to mutation via deamination of DNA bases.[7,8] Whereas γ-tocopherol protects against these damaging reactions, for example by reducing NO_2 to the more stable NO molecule, α-tocopherol reacts with the nitrogen dioxide radical to form a nitrosating agent, which in turn is capable of causing DNA damage.[6] Long-term exposure to radical damage associated with inflammation is believed to play a key role in cancer development.[9]

The chemistry of the tocopherols is mirrored by differences in their respective biological activities as well, such that γ-tocopherol is superior in preventing the formation of neoplastic cells,[6] is more protective against the cell killing effects of endogenous NO generation,[10] has greater anti-inflammatory properties,[11] and is more effective at inhibiting the growth of prostate tumor cells[12] and inducing apoptosis[13] than α-tocopherol. γ-Tocopherol also serves as the precursor to human natriuretic factor, which is formed through the cleavage of the long chain tail of γ-tocopherol by cytochrome P-450 3A.[14] On the other hand, α-tocopherol is superior in preventing oxygen-based radical damage[15] and possesses significantly greater Vitamin E bioactivity. It appears therefore that both tocopherol analogues may play important and distinct roles in human nutrition and health, both in terms of Vitamin E bioactivity and in the prevention of aging-related disease.

Recent epidemiological evidence supporting a role for the tocopherols in prostate cancer etiology is both compelling and intriguing. Helzlsouer et al.[16] in a cohort study of 10,456 men found that high serum γ-tocopherol was significantly inversely associated with

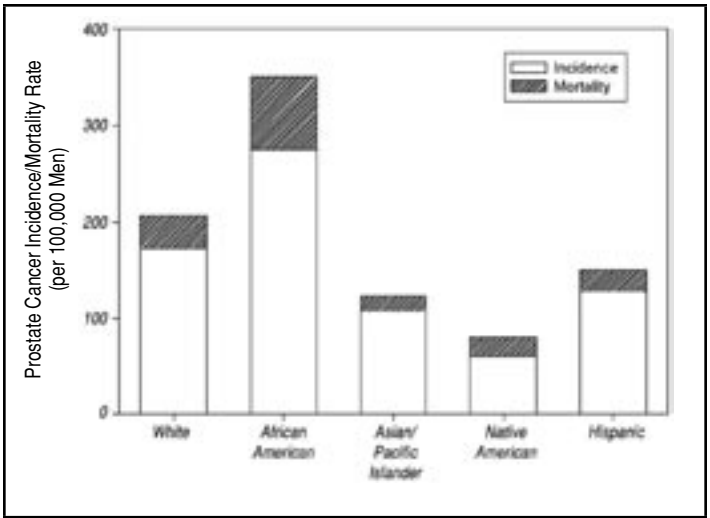

Figure 1.— Effect of ethnicity on incidence and mortality from prostate cancer.[1]

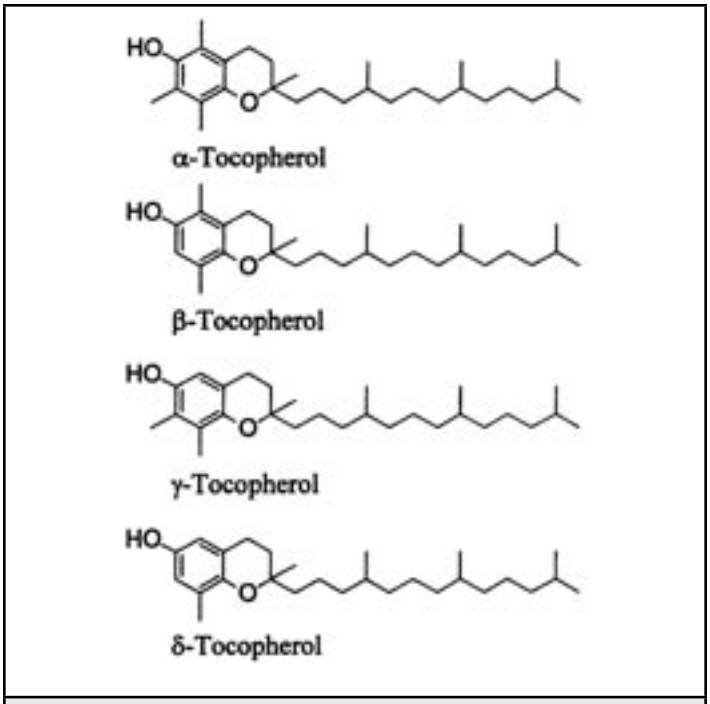

Figure 2.— Structures of naturally occurring tocopherols.

prostate cancer incidence, with nearly a five-fold reduction in risk for men at the highest levels of serum γ-tocopherol. In this study α-tocopherol was observed to be protective only in individuals with simultaneously high γ-tocopherol levels. Nomura, et al.[17] also reported a borderline protective effect for γ-tocopherol, however, the population examined did not possess serum levels of γ-tocopherol as high as the Helzlsouer study, perhaps reducing the power to detect a significant impact. Li, et al.[18] observed that α-tocopherol, but not γ-tocopherol, was highly inversely associated with prostate cancer in individuals with a particular polymorphism in the manganese superoxide dismutase gene resulting in a five-fold decease in risk for this particular population, whereas individuals without the phenotype showed little protection over the range of α-tocopherol concentrations observed.

The strongest evidence to date of a role for tocopherols in reducing prostate cancer incidence comes from a double-blind clinical prevention study in Finland involving >29,133 male smokers in which treatment with 50 mg/day of α-tocopherol resulted in significant reductions in prostate cancer incidence (32% decrease) and mortality (41% decrease) over seven years.[19] Support for a role of γ-tocopherol in this study was also found in an analysis of baseline serum values and subsequent development of prostate cancer in which a nearly 43% reduction in incidence was observed at the highest γ-tocopherol levels and 51% at the highest α-tocopherol levels.[20] Results from the clinical study in Finland have spurred additional clinical trials testing the efficacy of supplemental α-tocopherol, such as the SELECT Trial,[21] however, there is considerable concern that these trials, utilizing much higher doses of α-tocopherol (400 mg/day), may be fatally flawed, as there is little justification for utilizing such high doses and considerable reason to suspect that treatment at high levels may be counterproductive, as high dose supplementation with α-tocopherol significantly reduces serum levels of γ-tocopherol. Indeed, the recently completed HOPE trial, in which the effects of 400 mg/day of α-tocopherol on heart disease were assessed, demonstrated no protective effect with respect to heart disease or cancer and observed increased risk of heart failure in the Vitamin E-treated arm.[22] While such a result is not surprising in terms of what we know about the distinct chemical and biological effects of the different tocopherols, negative results such as these can have a chilling and counter productive effect on future studies of the optimal role of tocopherols in human health.

Clearly, well designed clinical trials testing the optimal levels of both α-tocopherol and γ-tocopherol in the prevention of prostate cancer incidence and mortality are warranted. However, we must avoid the mode of thinking that assumes that more of something "good" is always better. Instead we must utilize the information developed from *in vitro* and in animal models as well as epidemiologic and previous clinical trials to design trials that will definitively determine the optimal levels of these agents for maintaining health. This may require consideration of genetic differences between individuals in the way they respond as well, when the impact of these differences is known. At the same time the impact of other important micronutrients in prostate cancer cannot be ignored, such as selenium[23] which is incorporated into a number of important antioxidant enzymes capable of repairing certain types of oxidative damage. In particular selenium and the tocopherols may serve to complement each other in protecting from oxidative and nitrosative damage and imbalances in optimal levels of either may have adverse consequences. While the evidence is compelling for the tocopherols in the prevention of prostate cancer, we do not yet possess sufficient clinical information to make public health recommendations for supplemental intake, particularly for γ-tocopherol in which excessive levels may be deleterious.[4] However, given the severity of the impact of prostate cancer, properly designed clinical trials of these naturally occurring agents should be a priority of publicly funded research.

For more information on the Cancer Research Center of Hawai'i, please visit our Web site at www.crch.org.

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HAWAI'I MEDICAL JOURNAL

Issues in Medical Malpractice III

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University of Hawai'i

QUESTION: General practitioner (GP) delayed hospital admission for patient with chest pain who later died from myocardial infarct (MI). A close friend of the family heard the news over the phone several hours later and reacted with extreme grief. She later lapsed into prolonged depression that required psychiatric treatment.

A. GP is not liable to the patient because his chances of surviving the massive MI would at best have been 25%.
B. As a general practitioner, GP used his best judgment and should not be held to a higher standard.
C. GP is liable for the friend's injuries because he caused them.
D. GP is not liable to the family friend as there is no doctor-patient relationship.
E. Physical injuries are compensable, but psychiatric ones are not.

ANSWER: ***None correct***. All doctors, including general practitioners, are held to the standard ordinarily exercised by their peers. GPs are not held to the same standard as say, cardiologists, so the plaintiff would have to prove with expert testimony that a GP exercising reasonable care under similar circumstances would have promptly hospitalized the patient. Using one's best judgment may remove the moral culpability but it is not good enough to meet the legal standard. To win, the plaintiff will still have to prove proximate causation, i.e., the failure to hospitalize was both a factual and legal cause of the patient's demise. Although the likelihood of survival was 25% at best, many jurisdictions will consider this 'loss of a chance' as constituting sufficient causation. Both A and B are therefore incorrect.

Answers C, D, and E are also incorrect. It is true that there is no doctor-patient relationship between the doctor and the family friend, but this is not required in third-party allegations of negligent infliction of emotional distress. Liability for this tort requires proof of proximity in time and space, and a close relationship to the primary victim. A close relation is usually a family member and physical presence is needed to satisfy the proximity requirement. If these elements are present, there may well be liability even if the injured is a third party with no prior relationship to the tortfeasor (wrongdoer). The facts in this case do not seem to meet these criteria, so GP will likely escape liability to the family friend – but not because there was no doctor-patient relationship.

Finally, prevailing case law supports the notion that legitimate psychiatric conditions, such as depression, are compensable without need to show accompanying physical injuries. In the past, emotional injuries were thought to be difficult to define, so the courts had insisted that there be simultaneous physical injuries in order for a plaintiff to successfully claim damages.

Loss of a Chance

A patient may have lost the opportunity of avoiding or reducing harm because of the action or omission of the doctor. This is known as the 'loss of a chance' doctrine. In some jurisdictions, a defendant-doctor who deprives a patient of the chance, even if slim, of avoiding the injury may be held partly or wholly liable. Even if the lost chance did not reach a more-likely-than-not level, i.e., patient's chance of avoiding the risk was no better than 50%, some courts would still assess damages for all injuries that flowed from depriving the patient of that chance, whereas other courts would apportion the damages accordingly. Still others would deny the claim altogether.

In *Boody v. United States*, expert testimony established that the plaintiff had a 51% chance of five-year survival had her lung cancer been timely diagnosed. The court ruled that a plaintiff could recover for the loss of any appreciable chance, not just one exceeding 50% that resulted from a negligent act, in this case, failure to diagnose.[1] In another ruling, a Washington court held that the reduction in the chance of survival from 39% to 25% was enough to entrust the jury to decide on the issue of proximate causation.[2] The California Court of Appeals has framed the issue in a slightly different manner, reasoning that negligent treatment amounted to contributory factors that led to the plaintiff's death, even if the likelihood of survival was less than 50% to start out with.[3]

This article is meant to be educational and does not constitute medical, ethical, or legal advice. It is excerpted from the author's book, *"Medical Malpractice: Understanding the Law, Managing the Risk"* published in 2006 by World Scientific Publishing Co. You may contact the author, S.Y. Tan MD, JD, at email: siang@hawaii.edu or call (808) 526-9784 for more information.

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UPCOMING CME EVENTS

Date	Specialty	Sponsor	Location	Meeting Topic	Contact
September 2006					
9/8-9/9	ON, GO, SO	Cancer Research Center of Hawaii	Four Seasons Resort, Hualalai, Kailua-Kona	9th Annual West Hawaii Cancer Symposium	Tel: (808) 987-3707
9/21-9/22	Multi	Kaiser Permanente	Radisson Prince Kuhio, Honolulu	Palliative Care: An Interdisciplinary Approach	Tel: (808) 432-7932
October 2006					
10/2-10/4	Multi	Stanford Hospital & Clinics	Mauna Lani Bay Resort, Kohala Coast	Perspectives on Pain and Palliative Care	Tel: (650) 724-7166 Web: www.cme.stanfordhospital.com
10/9-10/12	PAT	Scientific Symposiums International	Princeville Resort, Princeville, Kaua'i	Learning to Make Those Gut-Wrenching Dermapathology Diagnoses	Tel: (925) 376-0217 Web: www.cme.stanfordhospital.com
10/12-10/16	R, N	Western Neuroradiological Society	Fairmont Orchid, Kohala Coast	38th Annual Meeting	Tel: (630)574-0220 x226 Web: www.wnrs.org
10/14-10/20	PD	University Childrens' Medical Group	Hyatt Regency Kaua'i Resort, Kaua"i	"Aloha Update" Pediatrics 2006	Tel: (800) 354-3263 Web: www.ucmg.org/cme.html
10/15-10/19	Multi	Ironman Triathlon World Championship	Royal Kona Resort, Kailua-Kona, Big Island, Hawai'i	18th Annual Official Ironman Sports Medicine Conference	Tel: (877) 843-8500
10/16-10/19	PAT	Scientific Symposiums International	Mauna Kea Resort, Big Island, Hawai'i	Surgical Pathology of Problem Breast & Endocrine, Female Genital -- Central Nervous System Lesions	Tel: (925) 376-0217 Web: www.scientificsymposiums.com
10/20-10-22	Multi	Hawai'i Medical Association	Hawai'i Convention Center, Honolulu	2006 Annual Meeting: Leading the Way… Building on 150 Years of Service	Tel: (808) 536-7702 Web: www.hmaonline.net
10/22-10/27	U	Western Section of the American Association of Urology	Hyatt Regency Resort, Maui	82nd Annual Meeting	Tel: (714) 550-9155 Web: www.wsau.org
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10/23-10/26	PAT	Scientific Symposiums International	Mauna Kea Resort, Big Island, Hawai'i	Critical Issues in Hematopathology, Infectious Disease, Laboratory Management, Reimbursement & Pathologist Compensation	Tel: (925) 376-0217 Web: www.scientificsymposiums.com
10/29-11/2	Multi	University of California, Davis	Grand Wailea, Maui	UCD Review and Update of Pain & Palliative Care Medicine	Tel: (916) 734-5390 Web: www.ucdmc.ucdavis.edu/cme
November 2006					
11/1-11/4	Multi	Symposia Medicus	Maui Prince Hotel at Makena Resort, Wailea	14th Annual Fall Conference on Issues in Women's Health	Tel: (800) 327-3161 Web: www.symposiamedicus.org
11/6-11/9	Multi	Kaiser Permanente	Wailea Marriott Resort	Evidence-Based Medicine Conference: The Essentials	Tel: (808) 432-7932
11/8-11/11	OBG	American College of Obstetricians and Gynecologists	Hapuna Beach Prince Hotel, Kohala Coast	Obstetrical and Gynecological Pearls	Tel: (800) 638-8444 x2540 Web: www.acog.org
11/12	PD	Lucile Packard Children's Hospital at Stanford	Mauna Lani Bay Resort, Kohala Coast	Prevention and Management of Childhood Obesity	Web: www.cme.lpch.org
11/13-11/15	PD	Lucile Packard Children's Hospital at Stanford	Mauna Lani Bay Resort, Kohala Coast	Popular Pediatric Clinical Topics	Web: www.cme.lpch.org

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References, from p.265

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❖ LIFE IS UNCERTAIN. EAT DESSERT FIRST.
Who would expect that the somewhat tranquil and wholesome field of ophthalmology would be the focus for a high profile crime with all the elements of a *CSI* or *Law and Order* television show including salacious testimony and a heinous crime. In Tucson, Ariz., a well-liked pediatric ophthalmologist with two children, Brian Stidham MD, was found murdered in the parking lot outside his medical office. Ten days later, the police arrested Bradley Schwartz MD, another pediatric eye surgeon, and charged him with first degree-murder and conspiracy to commit first-degree murder. Dr. Schwartz had a history of previous DEA arrest for writing fraudulent prescriptions, and underwent drug rehabilitation for addiction to *Vicodin* and *Ritalin*. He was accused of hiring a hit man, Ronald Bigger, to kill Dr. Stidham. The prosecution alleged that Dr. Schwartz hired Bigger to kill Dr. Stidham, his former partner, because he believed that Dr. Stidham was "stealing" his patients. One key prosecutor's witness, Lourdes Lopez, had been a Pima County prosecutor and had once been engaged to Dr. Schwartz. Other witnesses, including several girl friends, stated that Dr. Schwartz told them how much he hated Dr. Stidham and that he talked about killing him. The two-month trial ended in May and resulted in a guilty verdict on the conspiracy charge against Dr. Schwartz, but the judge declared a mistrial on the first-degree murder charge because the jury could not reach a unanimous decision. The prosecution has not decided whether to try him again. Meantime, there is probably a shortage of pediatric eye surgeons in Tucson.

❖ HYPOCHONDRIACS GET SYMPTOM RELIEF BY TAKING PLACEBOS.
Genentech Inc., has received Food and Drug Administration approval to market Lucentis, a drug that inhibits the growth of blood vessels when injected into the eye, and shows promise of preserving vision in cases of macular degeneration (AMD). Interestingly, the drug may actually compete with another Genentech drug, Avastin, a cancer treatment drug that has been used off label for two years to treat AMD. Both drugs block the same protein believed responsible for the blood vessel growth. One minor difference is that Lucentis costs $1,950 per dose while Avastin is $17 per injection. Genentech's chief medical officer thinks Lucentis is a much better choice. What a surprise!

❖ OVERLOAD IS THE DEMAND GEAR IN THE EMERGENCY DEPARTMENT.
A new national study recently released shows emergency department overcrowding is a nationwide concern. The report, headed by Dr. Brian Rowe, found that 82% of emergency department (ED) directors think overcrowding is having a serious negative impact on the nurses and physicians. Sound familiar? In this case, the report comes from the University of Alberta and describes the situation in Canada! The average wait time for a hospital bed in EDs is 11.1 hours, and that's the wait after the ED doctor has decided the patient needs to be admitted. Dr. Rowe states that the growing numbers of acutely ill patients held in emergency department is growing into a national crisis. To cite an old cliche, "Welcome to the Club."

❖ LIFE USED TO BE ONE THING AFTER ANOTHER. NOW THEY OVERLAP.
In what is believed to be a powerful testament to U.S. of A. health care improvements, the *National Center for Health Statistics* found that the annual number of deaths in this country dropped by about 50,000 in 2004, the largest such decline in more than 60 years. The last drop in deaths of this magnitude occurred in 1944 when the number dropped about 48,000 from the previous year. Overall, the 2004 data show age-adjusted death rates fell to a record low of 801 deaths per 100,000 population. The government added that life expectancy had inched up again to a record high of 77.9 years. And that is another old geezer bite out of the Social Security wallet.

❖ WHEN YOU DO A GOOD DEED GET A RECEIPT IN CASE HEAVEN IS LIKE THE IRS.
New guidelines have been issued by the *American Heart Association* (AHA) regarding cardio-pulmonary resuscitation (CPR). Previously we were taught to use 15 compressions for every two breaths. Now the number of compressions has been doubled to 30 for every two breaths. Studies show that the chest compressions create more blood flow through the heart to the rest of the body, but that after interruption with cardiac arrest, compressions must be built back up to obtain better perfusion. CPR is a critically important step in helping save lives since about 75% to 80% of cardiac arrests, such as drowning or electric shock, occur outside the hospital. More than 300,000 Americans die each year of cardiac arrest and the AHA estimates that 95% of those die before they get to the hospital. Effective CPR can double a victim's chance of survival.

❖ SHE WASN'T HIS TYPE – NOT INFLATABLE.
Wow! Talk about multi-tasking. Former Oklahoma district judge Donald Thompson is on trial on charges that he used a penis pump (this really happened) on himself in the courtroom while sitting in judgement of cases brought before him. For several days the white-handled sexual device sat for hours before the jury box, as both the defendant attorney and prosecutor pantomimed masturbation. The R-rated testimony caused surreal scenes and outbursts of laughter, particularly when a urologist expert witness explained the use of the device. It was claimed to be an out-dated device for erectile dysfunction, but the urologist said, "I still use those," then explained to a laughing jury, "No, as a urologist, I recommend those." Court reporter Lisa Foster wiped away tears as she described having seen the judge expose himself at least 15 times when she heard the familiar "sh-sh" in the courtroom. "I was really shocked and I was kind of scared because it was so bizarre." The judge is charged with four counts of indecent exposure and, if convicted, he would have to register as a sex offender, and could lose his $7,489 monthly pension. He should have seen that coming.

❖ WHAT THE GULF COAST NEEDS NOW IS GATOR-AID.
The *Wall Street Journal* reports that additional fall-out from hurricane Katrina is a decrease in alligator harvesting on the gulf coast. Women's handbag designers are busily searching for sources as prices of alligator hides have spiked to 50% what they were two years ago. Ralph Lauren has had to raise the price of its most prestigious gator handbag to $14,000. Alligator shoes, shirts and coats have jumped in price as well, and Giorgio's of Palm Beach raised the asking price of its alligator paneled piano to $950,000. Oh, the suffering!

❖ THE USMC ADMONITION TO CHANGE SKIVVIES EVERY THREE WEEKS IS OUTDATED.
You could be a walking, talking source of trouble for your patients. The *Board of Science of the British Medical Association* recommends that you should thoroughly launder your work clothes and keep them separate from the rest of your wardrobe to reduce the spread of infectious disease. Moreover, doctors should stop wearing clothes or outer wear that do not serve function, especially neckties. Too often they are rarely washed, and may be worn in and outside the health care environment. In short, doctors and others working in hospitals and clinics can easily become reservoirs for some ugly disease.

❖ THE MIDGE IS NOT A VEGETARIAN.
In the area of solving one problem to produce another, Scottish pubs are now investing in anti-midge machines. Midges do not like tobacco smoke, and with the new law outlawing smoking in pubs, swarms of midges have arrived to bite customers and staff. Fortunately, the "midge machine" creates a smell of animal's breath which midges seek, and they are lured to their death in large numbers.

❖ HEY, DUDE! DON'T LET THE COOLER TIP OVER.
In Cottage Grove, Minnesota, a 38 year-old man was spending the afternoon golfing and drinking. He managed to crash his golf cart which resulted in his golfing buddy being pinned under the cart. He suffered head injuries requiring hospitalization. The cart driver had a history of a previous DUI conviction (presumably on the highway), and his BAC was 0.24. The police charged him with criminal vehicular operation, punishable by up to three years in prison. His lawyer did not contest the facts, but defended the driver by claiming that since his golfing friend did not file a complaint, it was wrong for the police to do so.

ADDENDA
❖The first sperm banks were opened in 1964; they were in Tokyo, Japan, and Iowa City, Iowa.
❖There is enough phosphorous inside the average human to make about 250 matchheads.
❖As long as there are tests, there will be prayer in public schools.
❖Procrastinate now - don't put it off.

ALOHA AND KEEP THE FAITH — **rts**■

Contents of this column do not necessarily reflect the opinion or position of the Hawai'i Ophthalmological Society and the Hawai'i Medical Association. Editorial comment is strictly that of the writer.

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