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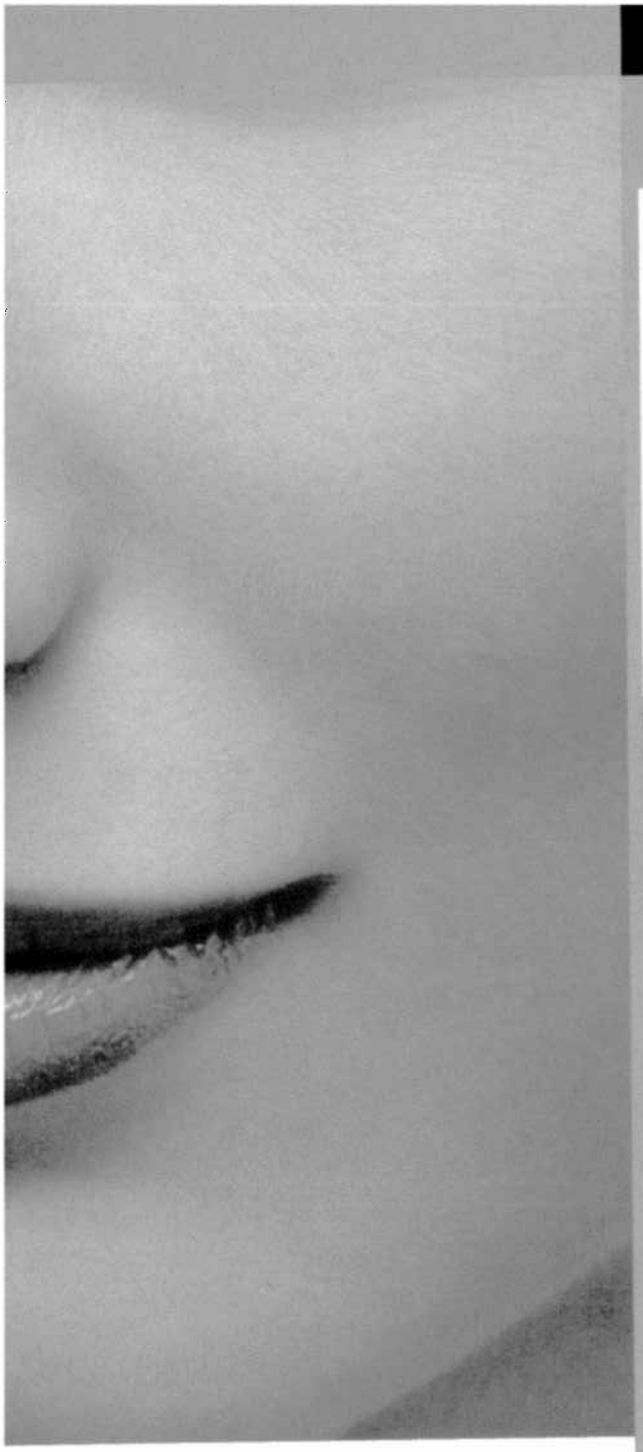

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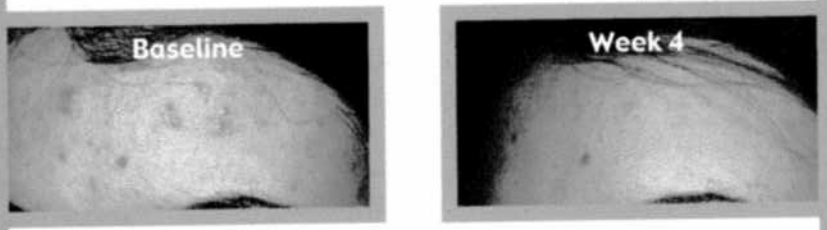
- With once-a-day Duac™ Topical Gel, visible results were demonstrated in just 4 weeks[1]

Unretouched photos of patient treated with Duac Topical Gel once daily.



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- The first and only second-generation benzoyl peroxide/antibiotic combination therapy
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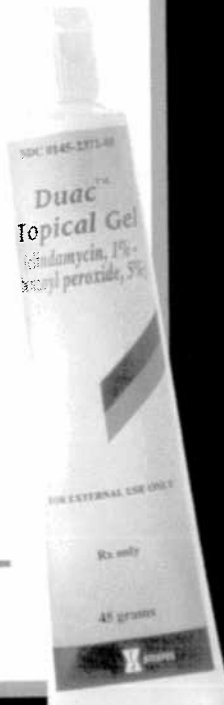
Duac Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and colitis [including pseudomembranous colitis] have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Please see following page for Brief Summary of Prescribing Information.



once-a-day Duac™ topical gel

(clindamycin, 1% - benzoyl peroxide, 5%)

DU it differently™

STIEFEL®

Research in Dermatology

*Duac Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months.
[1]Data on file, August C. Stiefel Research Institute, Inc.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Duac™ Topical Gel

(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.

Rx Only

INDICATIONS AND USAGE
Duac Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Duac Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS
Duac Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS
ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium difficile* AND STOOL ASSAY FOR *Clostridium difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS
General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using Duac Topical Gel should receive the following information and instructions:

1. Duac Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician.
5. Duac Topical Gel may bleach hair or colored fabric.
6. Duac Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying Duac Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with Duac Topical Gel or benzoyl peroxide. It is also not known whether Duac Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

Local reactions with use of Duac Topical Gel
% of patients using Duac Topical Gel with symptom present
Combined results from 5 studies (n = 397)

	Before Treatment (Baseline)			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled Duac subjects, n = 397).

HOW SUPPLIED
Duac™ (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

Dispensing Instructions for the Pharmacist: Dispense Duac Topical Gel with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."

Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637
Patent Pending

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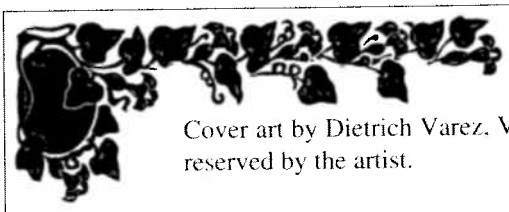

Cover art by Dietrich Varez, Volcano, Hawaii. All rights reserved by the artist.

Keiki Ho'okama

In old Hawaii the pig was often loved as a pet.

Do All Drugs have to be Destroyed at the Expiration Date?

Norman Goldstein MD
Editor, Hawaii Medical Journal

Hypothetically, your patient brings in a bag of medications he is taking. You look at the expiration dates when he says, "I guess I have to throw these out now and buy new ones."

No, he does not necessarily have to discard all those dated meds. According to Joel Davis, former FDA expiration-date compliance chief, "most drugs degrade very slowly. In all likelihood, you can take a product you have at home and keep it for many years, especially if it's kept in the refrigerator."[1] (an important factor in Hawaii, Ed.)

Notable exceptions include nitroglycerine, insulin and some liquid antibiotics. Topical products like creams, ointments, solutions and gels may also be exceptions.

A Medline search for adverse reactions to outdated drugs found only one report. In 1963 a reversible "Fanconi Syndrome" caused by degraded tetracycline was reported in three patients.[2] The syndrome of reduced renal function, acidosis, proteinuria glycosuria and aminoaciduria was found in a 54-year-old widow of a physician and a 13 year-old girl and boy. All three recovered. It was proposed that a degradation product of tetracycline, perhaps epianhydrotetraclycine or anhydrotetracycline was the probable etiologic factor.

Considering the vast amount of tetracycline and tetracycline-related products that have been prescribed over the past forty years since this paper, no other reports of adverse reactions have been published.

The Medline search performed by the Reference Section of the Hawaii Medical Library did find several Letters to the Editor (some of them anonymous) and articles dealing with policies pertaining to expired drugs in diverse publications including Advances for Nurse Practitioners, Journal of the American Veterinary Medical Association, Australian Veterinary Journal and one in the American Journal of Hospital Pharmacy entitled "Expired Drugs are not Dead Drugs."[3]

The Air Force and more than One Billion Dollars of Stockpiled Drugs

In 1981, in order to increase readiness, the US military bought large quantities of drugs and medical devices. The General Accounting Office audited Air Force hospitals in Europe and found many supplies had expired or were near expiration. The GAO warned that by the 1990s more than one hundred million dollars would be required yearly for replacement.

The FDA, at the request of the Air Force Surgeon General's Office, started a study in 1985 with 58 medicines from 137 different marketing lots including penicillin, Lidocaine and Lactated Ringer's Solution. After testing, the FDA extended more that 80% of the expired lots by an average of 33 months. In 1992, more than half of the expired drugs that had been tested in 1985 were still effective.

So why not enable the use of medicines after the expiration date? Some claim newer, more beneficial drugs can be brought on the market more easily if the old ones are discarded after a few years. Pharmaceutical companies do not agree with this premise.

Mark van Arandonk, senior director for pharmaceutical development at Pharmacia & Upjohn Inc. said that "two to three years gives us enough time to put inventories in warehouses, ship and ensure it will stay on shelves long enough to get used."[1]

Because of the emphasis on discarding expired medications, some underdeveloped countries are refusing to accept perfectly safe and effective drugs. The problem of expiration dates on drugs should be a point in the prescription drug plan before Congress at this time. Congress needs input not just from the pharmaceutical companies, researchers and pharmacists. It needs to hear from you, the practicing physician. Expired medicines are not dead. Let's not bury them, but put them to good use.

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NHCOE Summer 2003 Conference: Prelude to *Festschrift*

William W. Goodhue Jr. MD
Associate Editor, Hawaii Medical Journal

The John A. Burns School of Medicine (JABSOM)'s Native Hawaiian Center of Excellence (NHCOE) held its Summer 2003 Conference on July 26-27 at the JW Marriott Ihilani Resort and Spa at Ko Olina. Fifty-eight attendees and their families from Oahu and the neighbor islands at this *Tribute to Drs. OA Bushnell and Charles S. Judd, Jr.* heard 17 distinguished speakers, two coming from as far as Atlanta and Bethesda, reminisce about Ozzie and Charlie, discuss the impact of infectious (including emerging) diseases on our world and local communities and identify new medical and surgical challenges facing *kanaka maoli*. A faculty development workshop rounded out the program. Mary, widow of Charlie Judd, was an honored guest at the Conference. Betty Bushnell was unable to attend. The Conference was sponsored by the Hawaii Consortium for Continuing Medical Education, a joint venture between the Hawaii Medical Association (HMA) and JABSOM. The NHCOE is supported by a grant from the Department of Health and Human Services.

Ozzie Bushnell and Charlie Judd, well-known to our *HMJ* readership, were giants in our midst. Ozzie combined a scientific background, love of history and literary panache to produce some of Hawaii's finest and most popular books. He died in 2002. Charlie, whose Pacific peregrinations in the Navy during World War II spawned an enduring love for islanders, was the scion of a *kamaaina* family. He was a surgeon whom the Samoan government honored for his work there with an award previously only given to Robert Louis Stevenson. His contributions to the Oahu community were legion. He was Chairman of the JABSOM Department of Medical History at the time of his death in 1987 and previously had been named Hawaii's Physician of the Year. Photographs of Drs. Bushnell and Judd at various times in their lives were displayed in the conference room. Pictures from the JABSOM yearbook *Kahuna* of many attendees also were projected at unexpected times during the presentations!

Edwin C. Cadman, MD, JABSOM Dean, provided opening remarks commending the NHCOE for seeking to identify and correct health disparities between *kanaka maoli* and other ethnicities. He said that Conference presentations would provide stimuli to achieve these objectives. **Benjamin BC Young,** MD, NHCOE Executive Director, related anecdotes about Ozzie and Charlie in his introductory remarks, echoed Dean Cadman's announcement that the National Institutes of Health (NIH) had awarded the University a grant endowing a Chair of Medical History honoring former Bishop Estate Trustee Myron "Pinky" Thompson and said that after this Conference there would be a call for papers for a *festschrift*, an *HMJ* commemorative issue, honoring Ozzie and Charlie. Director Young's objective is to secure funding to endow a *Charles S. Judd, MD and OA Bushnell, PhD Endowed Chair of Hawaiian Medical History*. **Martina Kamaka, MD,** NHCOE Faculty and Curriculum Development Coordinator, introduced each of the speakers.

The Saturday morning session was *A Tribute to Ozzie Bushnell: Infectious Diseases*. **D. Peter Drotman, MD, MPH,** Centers for Disease Control and Prevention, Atlanta GA, and Editor-in-Chief, *Emerging Infectious Diseases*, elaborated on *My Life and Hard Times in Infectious Diseases from the Last Cases of Smallpox and the First Cases of AIDS to Emerging Infectious Diseases*. **Paul Effler, MD, MPH,** State Epidemiologist, applied Dr. Drotman's comments in *Emerging Infectious Diseases: Hawaii Status Report/ What Physicians Need to Know*, in which he discussed epidemiology in *Hawaii nei* of dengue, murine typhus, antibiotic-resistant gonorrhea, *Campylobacter* and influenza. He noted that none of the few suspected cases of Severe Acute Respiratory Syndrome (SARS) investigated here were confirmed. An *Update on Infectious Diseases in Native Hawaiians* rounded off the morning. **Wayne Kyono, MD,** Assistant Professor, Pediatrics, JABSOM, presented his research and clinical work on *Impaired Neutrophil Function & Invasive Bacterial Infections in Pacific Islander Children*. **Guliz Erdem, MD,** Assistant Professor, Pediatrics, JABSOM, examined reasons in her *Acute Rheumatic Fever in Hawaiians and Pacific Islanders* why Polynesians are particularly susceptible to this sequela of Streptococcal infection. **Anthony Guerrero, MD,** Associate Professor, Psychiatry and Pediatrics, JABSOM, hypothesized in *Neuropsychiatric Post-Streptococcal Infections (OCD)* that the high prevalence of obsessive-compulsive disorder among Hawaiian adolescents may represent instances of PANDAS (*P*ediatric *A*utoimmune *N*europsychiatric *D*isorders *A*ssociated with *S*treptococcal *I*nfections).

David Morens, MD, NIH, Bethesda MD raconted during lunch his recollections of his teacher Ozzie Bushnell and discussed *Death in the Cannibal Islands, 1875: An Infectious Confrontation between Pacific Civilizations*. Introduction of measles that year by return from Australia of the infected Fijiian royal family reduced the native

Continued on p. 176

Adverse response to pegylated interferon therapy in two patients with chronic hepatitis C

William L. Thomas Jr. MD, Fernando Ramos MD, and Duane R. Hospenthal MD, PhD

Disclaimer: The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Abstract

Pegylated interferons have recently been approved for treatment of hepatitis C. The safety of these formulations is reported to be similar to that of non-pegylated interferon. We present two patients who experienced exacerbations of their liver disease following administration of pegylated interferon alfa-2b. Vigilant monitoring of patients treated with these new agents is recommended.

Introduction

Hepatitis C virus infects almost 200 million people worldwide.[1,2] In the US, chronic hepatitis C is estimated to affect nearly four million people. Recently, the FDA has approved two formulations of pegylated interferon, pegylated interferon alfa-2b (PEG-Intron®, Schering) and pegylated interferon alfa-2a (PEGASYS®, Roche) for therapy of hepatitis C, increasing the therapeutic options available to treat this disease. Studies have shown the safety profiles of both pegylated and non-pegylated interferons to be similar.[3,4,5] Although adverse effects are common with interferon therapy, no severe adverse effects unique to the pegylated form of this drug have been described. We report two cases of adverse effects seen with the use of pegylated interferon alfa-2b.

Case 1

A 78-year-old Asian male was referred to our department for evaluation of chronic hepatitis C, genotype 1a. Prior to initiation of treatment, his laboratory tests showed the following: alanine aminotransferase (ALT) 241 U/L (normal range [NR] 0-40), aspartate aminotransferase (AST) 117 U/L (NR 0-37), total bilirubin (TB) 1.0 mg/dL (NR $\leq$1.0), hepatitis C viral load by RNA PCR testing (HCV RNA) 107,300 copies/mL, hepatitis B surface antibody (anti-Hbs) and total hepatitis A antibody (anti-HAV) positive. A biopsy of his liver showed chronic hepatitis with mild steatosis, grade 3 inflammatory changes and stage 3 fibrosis. He was started on combination therapy of interferon alfa-2b, 3 million units by subcutaneous injection three times weekly, and oral ribavirin 1000 mg daily (Rebetron®, Schering, Kenilworth, NJ).

The patient did not tolerate the combination treatment secondary to ribavirin-induced hemolytic anemia despite trials of dose adjustments and erythropoietin. Thus, the ribavirin was stopped and he was continued on monotherapy with interferon alfa-2b. Twenty-four weeks into his therapy, the patient was noted to have normal transaminases and undetectable serum HCV RNA. Following the FDA approval of pegylated interferon alfa-2b (PEG-Intron®, Schering, Kenilworth, NJ), he was switched to this product at a dose of 50 mg (1.0 μg/kg) weekly. The first dose was given two days following his last dose of non-pegylated interferon.

Laboratory evaluation after two doses of this new therapy revealed an AST of 28 U/L and an ALT of 20 U/L. After the sixth dose ALT increased to 469 U/L. Repeat testing after his seventh dose revealed an AST of 312 U/L, an ALT of 602 U/L, and HCV RNA was 351,000 copies/mL. Given these results, treatment with pegylated interferon was discontinued. During these seven weeks of pegylated interferon therapy, patient reported only other medication to be a single daily multivitamin. He denied used of other prescribed, over-the-counter, herbal medicines or health supplements.

Thirteen days after his last pegylated interferon dose, his AST had decreased to 171 U/L and ALT to 376 U/L. By 21 days, AST and ALT were 79 U/L and 204 U/L, respectively. After one month AST and ALT were 39 U/L and 64 U/L, respectively. The patient was started back on monotherapy with non-pegylated interferon alfa-2b and his transaminase levels have subsequently returned to normal limits. Repeat antinuclear antibody (ANA) and anti-smooth muscle antibody were negative. His albumin prothrombin time (PT) remained normal throughout all treatments.

Case 2

A 49-year-old Caucasian male with chronic hepatitis C, genotype 1b, who had not responded to a previous trial of combination interferon alfa-2b and ribavirin, was referred to our center for further evaluation. Liver biopsy done two years previously revealed grade 3 inflammation and stage 3 fibrosis. Treatment with 1.0 μg/kg body weight/day of subcutaneous pegylated interferon alfa-2b was started with the goal of preventing progression of fibrosis and decompensation of his liver disease. Medications prior to treatment initiation included citalopram and ranitidine. Patient denied use of other prescribed, over-the-counter, herbal medicines or health supplements immediately prior to, or following his single dose of pegylated

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interferon. Before this treatment, his laboratory values included ALT 56 U/L (NR 0-40), AST 93 U/L (NR 0-37), TB 2.4 mg/dL (NR < 1.0), alkaline phosphatase (ALP) 103 U/L (NR 38-126), PT 12.8 seconds (NR 10.4-12.7), HCV RNA >1,000,000 copies/mL. No ascites or encephalopathy was evident.

After his first and only dose, his ALT and AST increased to 71 U/L and 133 U/L, respectively, and his TB doubled in value. Treatment was stopped after this first dose and repeat testing two weeks later revealed ALT 84 U/L, AST 124 U/L, and TB 7.4 mg/dL. These abnormalities peaked one month after treatment at ALT 207 U/L, AST 156 U/L, TB 8.0 mg/dL, and PT 13.2 seconds. The patient's only complaint was severe pruritis throughout this time period. No ascites or encephalopathy was evident. Treatment with ursodiol 600 mg orally twice daily was started with subsequent rapid improvement in symptoms and liver test abnormalities. Three weeks after initiation his laboratory results revealed ALT 91 U/L, AST 102 U/L, TB 2.8 mg/dL, and PT 12.4 seconds. Evaluation for other causes of acute hepatitis was unrevealing: hepatitis B surface antigen (HbsAg) nonreactive, anti-HAV IgM negative, hepatitis B core (anti-HBc) IgM negative, ANA negative, monospot negative, anti-smooth muscle antibody nonreactive, and anti-CMV IgM negative. No abnormalities of his serum albumin or ALP were noted during the course of his disease and right upper quadrant ultrasound done during bilirubin elevation was unremarkable.

Discussion

Two formulations of pegylated interferon are now available for the therapy of chronic hepatitis C, PEG-Intron®, a covalent conjugate of recombinant interferon alfa-2b with a 12 kilodalton (kd) polyethylene glycol (PEG) moiety, PEGASYS®, a conjugate of interferon alfa-2a and a branched 40 kd PEG chain.[3] Interferon is believed to work by binding to cell surface receptors and initiating a sequence of intracellular events which result in suppression of cell proliferation, inhibition of viral replication in virus-infected cells, and enhancement of the phagocytic activity of macrophages and the cytotoxicity of lymphocytes for target cells. Pegylation of interferon results in decreased clearance and thus an increase in mean half-life compared to non-pegylated drug, allowing once-weekly dosing without the prolonged serum troughs seen with non-pegylated drug. The sustained levels obtained with pegylated drug likely account for the greater efficacy of these compounds. Adverse effects of once-weekly dosed pegylated interferons have been similar to those of thrice-weekly non-pegylated drug. Common adverse effects include "flu"-like symptoms - fatigue, headache, myalgias, rigors, pyrexia, and nausea. Laboratory abnormalities occur less frequently, the most common being neutropenia, followed by thrombocytopenia and anemia. Other important adverse effects include anorexia, neuropsychiatric symptoms including insomnia, irritability, and depression, and alopecia. Adverse effects or laboratory abnormalities severe enough to warrant cessation of drug occurred in 6-11% of subjects in two of the largest trials of pegylated versus non-pegylated interferon.[4,5] The only adverse effect seen more frequently with pegylated drug appears to be injection site inflammation. Elevation of ALT of 2-5 times above baseline was seen in 10% of patients treated with PEG-Intron® in pre-marketing trials.[6] These elevations were transient and were not associated with deterioration of other liver functions. Hyperbilirubinemia was reported in 10-14% of those patients receiving combined therapy with interferon alfa-2b and ribavirin.

Case 1 may be the first case in the literature of severe worsening of hepatitis following the initiation of pegylated interferon. His ALT, while only 2.5 times his pretreatment level, rose 30 times that of the level seen on non-pegylated interferon therapy. The marked elevation in ALT and loss of HCV RNA suppression after starting PEG-Intron® indicates liver injury and uncontrolled replication of the virus. The cause of this severe worsening on change of interferon therapy is unclear but could possibly be due to an autoimmune mechanism, or less likely to another infection or intoxication we did not identify.

Case 2 demonstrates acute cholestasis following administration of PEG-Intron® as manifest by the increase in both ALT and serum bilirubin. These indices trended toward the normal range after the prompt removal of the drug and treatment with ursodiol. The marked improvement with ursodiol treatment was surprising and encouraging. Further studies are needed to evaluate the role of this medication in patients with acute hepatic injury due to pegylated interferon. No other cause for the acute abnormalities in this person was identified. These cases represent the first report of severe adverse liver reactions to the pegylated interferon, PEG-Intron® in its use in the treatment of hepatitis C. Other likely causes of exacerbation were ruled out in these cases leaving the only obvious variable in each case the introduction of this new drug. These results call for vigilant monitoring of patients treated with pegylated interferons, especially PEG-Intron® and prompt withdrawal of these drug in patients who demonstrate an acute increase in ALT.

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Descriptive epidemiological analysis of diving accidents in Hawaii from 1983 to 2001

Harumi Nakayama MD, PhD and Richard W. Smerz DO, MTMH*

Abstract

The Hyperbaric Treatment Center (HTC) at the University of Hawaii, has evaluated and treated over 1100 divers for dysbaric disease from 1983 to 2001. We describe some epidemiological parameters and compare trends between local residents and tourist divers in this article. Data obtained from this review were analyzed for age, gender, type of injury and resident status. While trends in Hawaii have mirrored national figures, we did determine that there were some significant differences between resident and tourist divers' patterns of injury over this period of time.

Introduction

As an island state located in the mid-Pacific Ocean, Hawaii attracts thousands of visitors each year who come to partake of the aloha spirit, the warm, balmy climate, and an amazing number of scenic wonders and activities. Scuba diving, one such activity, has been increasing in popularity as a recreational enterprise since it was introduced.

Hawaii also has many residents whose employments, as well as recreational interests involve diving. Participation in this activity exposes these divers to some unique risks as a consequence.

In 1983, in response to the growing interest in scuba diving in the islands, and the anticipated need for treatment of potential diving injuries, the State of Hawâii established the Hyperbaric Treatment Center (HTC). Since its inception through 2001, the HTC has treated over 1100 patients for dysbaric disease. Several studies describing the frequency and types of diving injuries, treatment modalities, and treatment complications in Hawaii have been conducted.[1-4] This paper will describe some of the epidemiological characteristics and parameters of the total patient population evaluated at the HTC, and compare trends between resident and tourist divers.

Methods

A retrospective chart review was conducted in 2002 on patients who presented to the HTC for suspected diving related injuries. Data obtained from this review were analyzed looking at age, gender, type of injury (AGE or DCS), site of accident, and resident status (local vs. tourist) using Microsoft Access and Excel. Graphic representation of these data were produced and subjected to trend analysis. Variables were analyzed using the chi-square test (significance level = 0.001).

Results

Over the study period, a total of 1192 patients were evaluated for potential dysbaric injury. Figure 1 depicts the number of cases seen per year. The average number of cases per year was 63. Peak injury years were from 1991 through 1996 where the average number of cases per year was 88. Male divers have represented the majority of cases each year except in 1990 and 1993, but the trend has steadily moved towards gender parity (Figure 2). Residency status was clearly defined in 1110 of these patients. Local residents constituted the majority in every year and totally (736 cases, 66%), but since 1990, tourists (374 cases, 34%) have steadily increased from 30 to 47 per cent of the caseload (Figure 3). Of the total number of 1192 patients evaluated for dysbaric disease, 866 were determined to have either an Arterial Gas Embolism (AGE) or Decompression Sickness (DCS), which required recompression treatment. The total number of AGE cases was 100 (11.5%), while the total number of DCS cases was 766 (88.5%) (Figure 4). When comparing injury type versus resident status (Table 1), there was little difference between the two groups with respect to DCS occurrence (residents- 91.7%; tourists- 83.3%), but when looking at the AGE cases, tourists suffered this disorder at twice the rate of residents (16.7% vs. 8.3% p= 0.001). Among residents, 4-5 times as many males were injured as compared to females, while in the tourist population, males constituted nearly 60% and females were just below 40% (Table 2). Female tourists had twice the injury rate of resident females (Table 2). The age for defined injury cases averaged 34.4 years (range 12-77) with most cases occurring in the 21-40 year age group (Figure 5). Since 1996, there has been a gradually increasing trend in the number of the older than 41 age group. Of note is the fact that tourists under age 20 had an injury rate double that of resident cases in the same age group (Table 3).

When evaluating site of injury, most cases originated from Oahu (49.2%), followed by Maui (23.3%) and Hawaii (15.6%). Residents were more often injured on Oahu while tourists were more often injured on Maui (Figure 6).

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Figure 1.— Distribution of cases from 1983 to 2001 (n=1192)

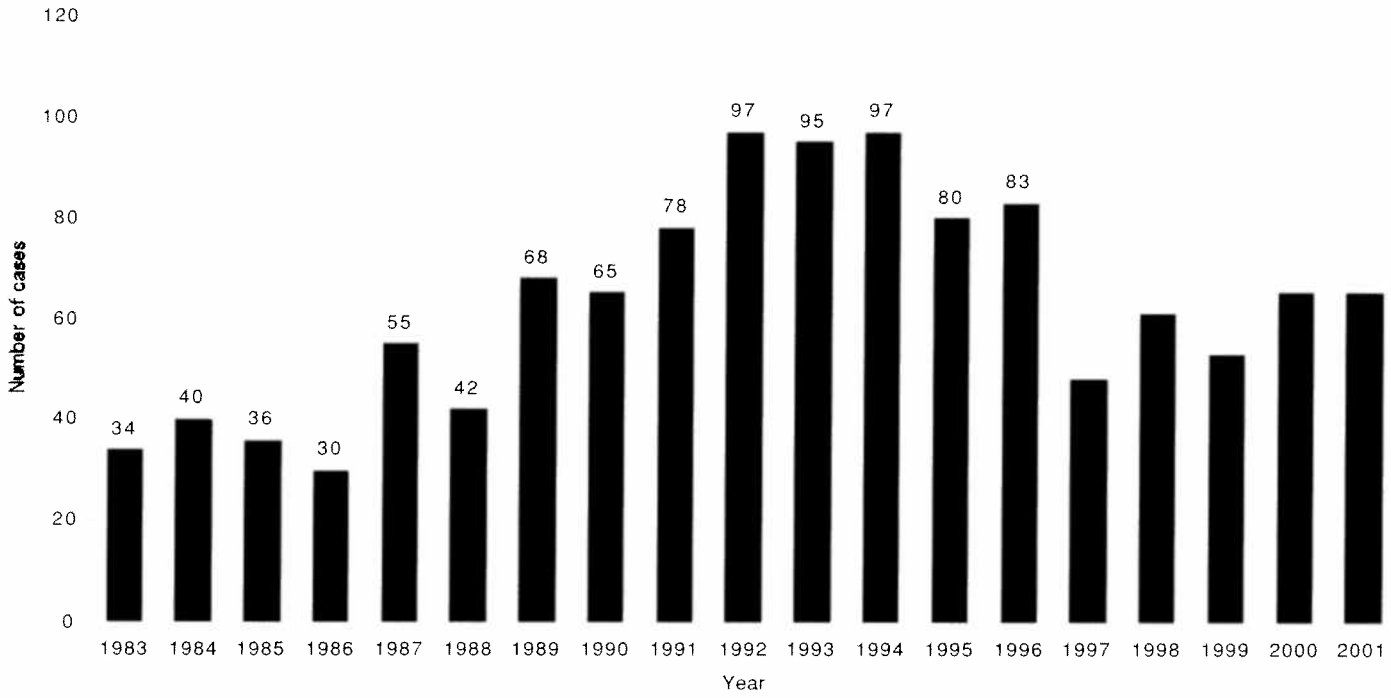

Figure 2.— Ratio of each gender cases from 1983 to 2001 (n=1192)

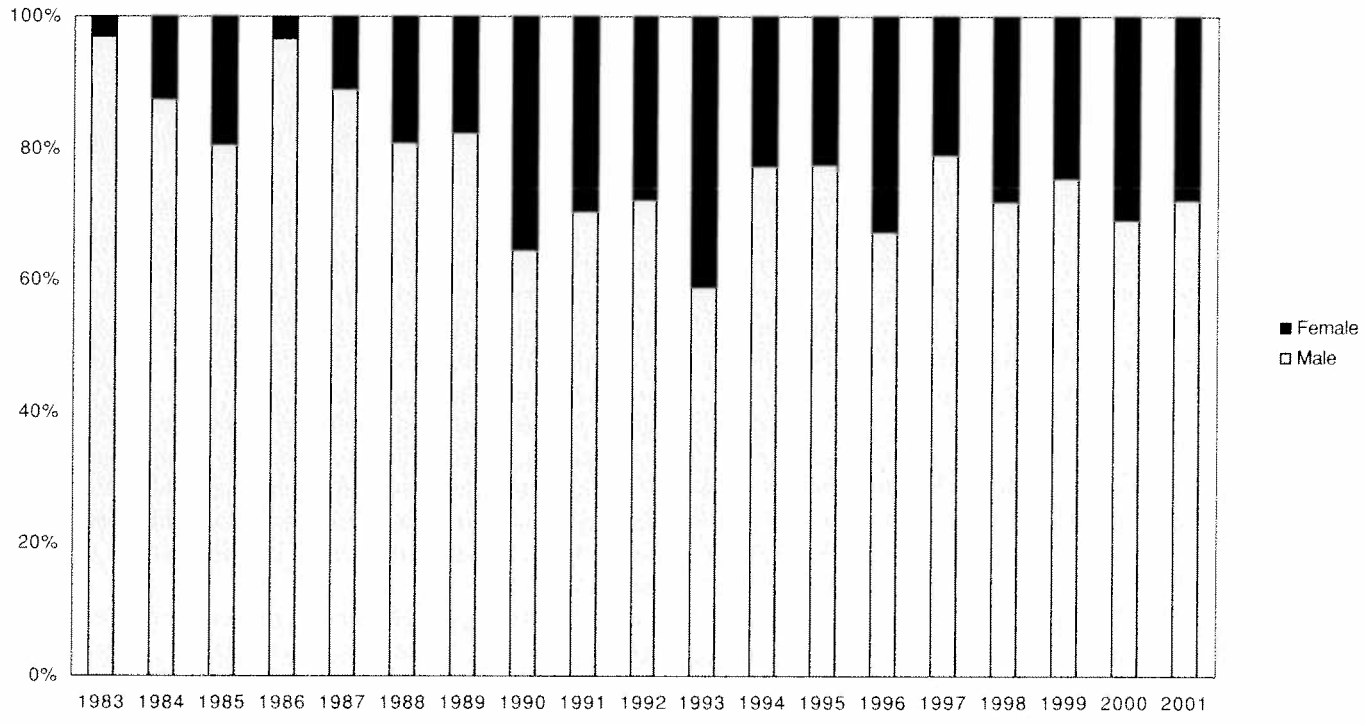

Figure 3.— Ratio of each residential status cases from 1983 to 2001 (n=1110)

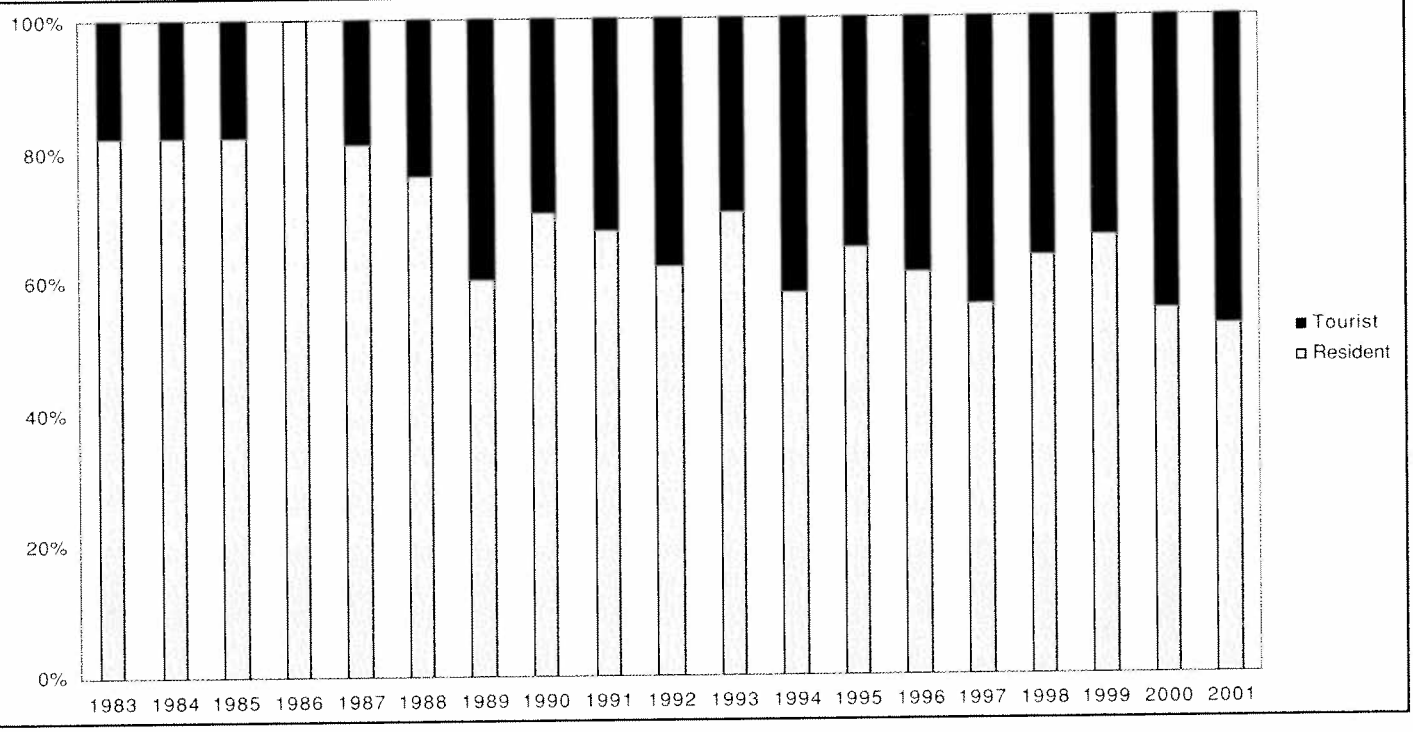

Figure 4.— Ratio of DCS cases and AGE cases from 1983 to 2001 (n=866)

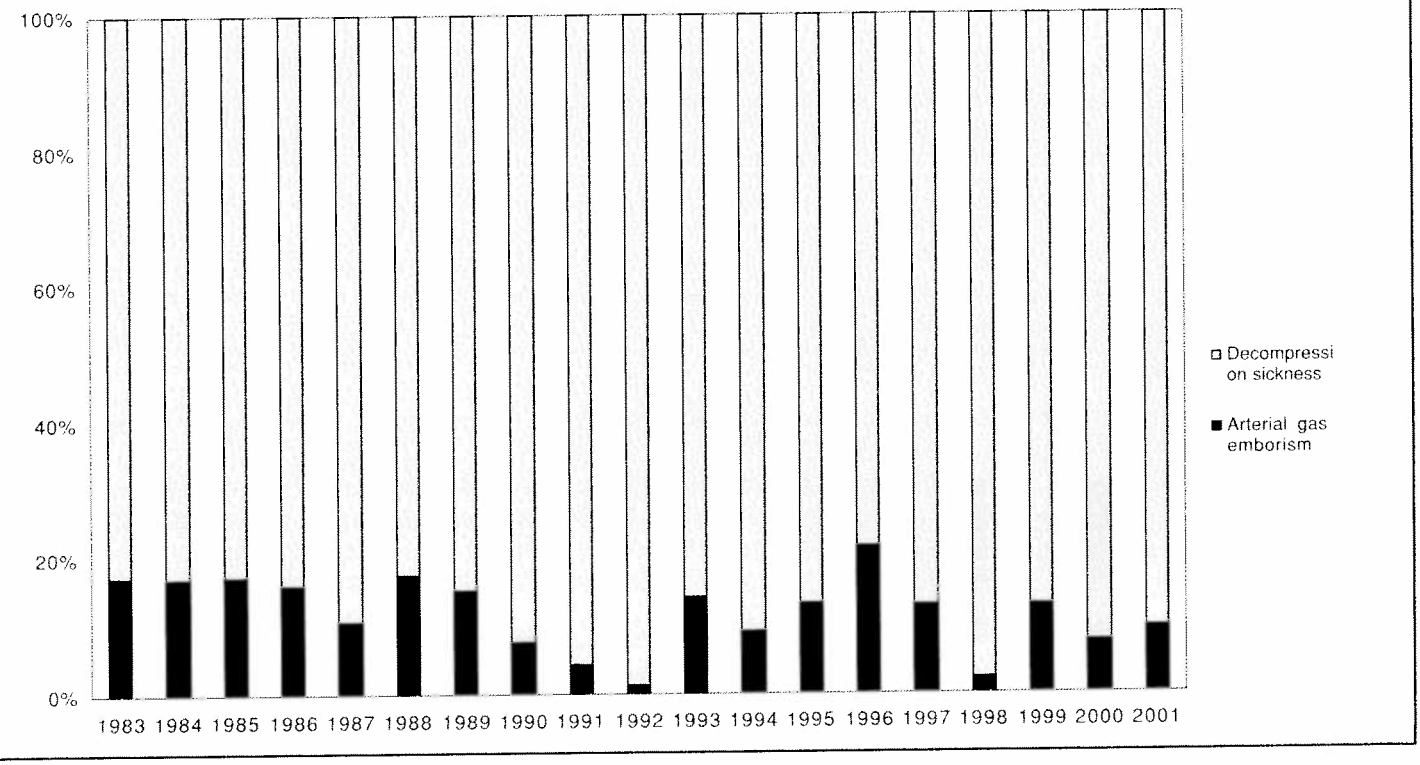

Figure 5.— Ratio of each age groups from 1983 to 2001 (n=857)

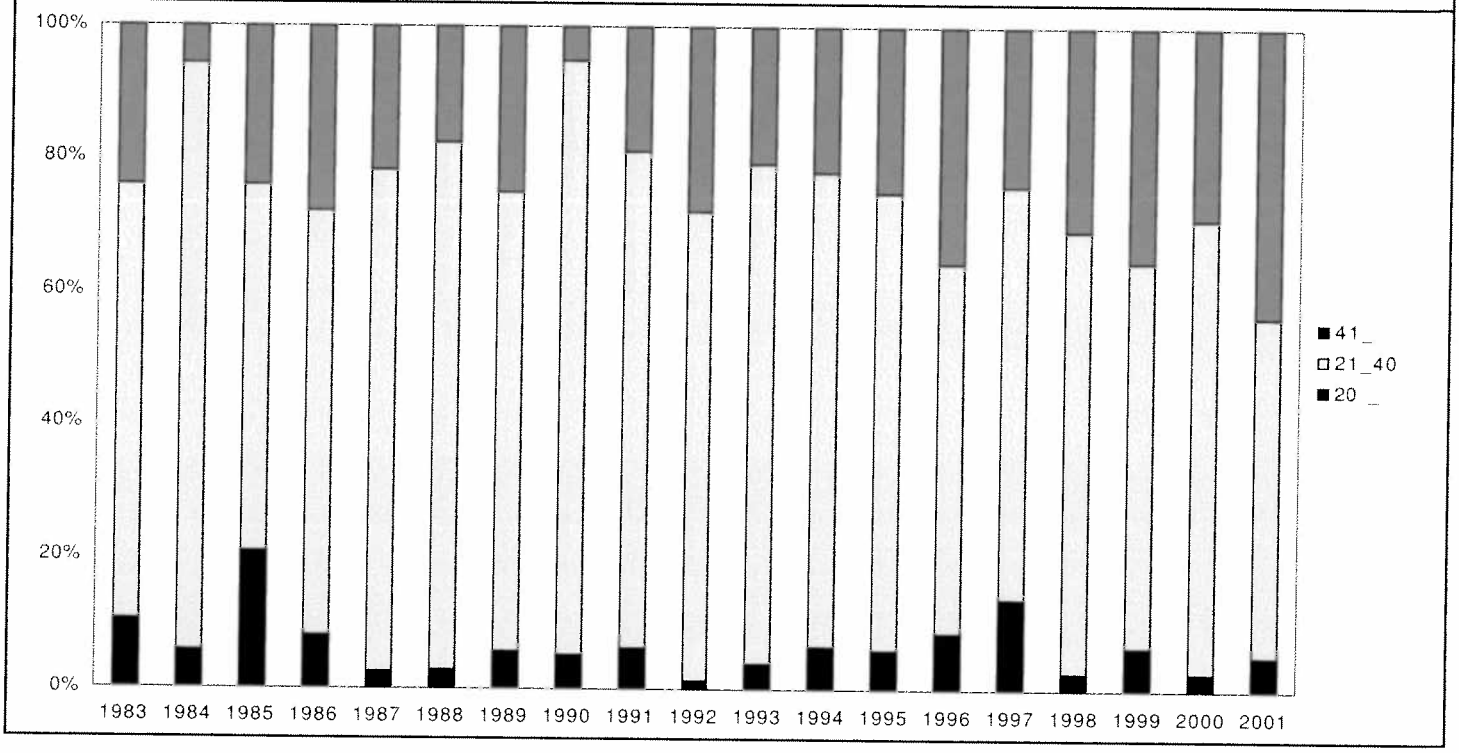

Figure 6.— Site of injury between residents and tourists (n=1009)

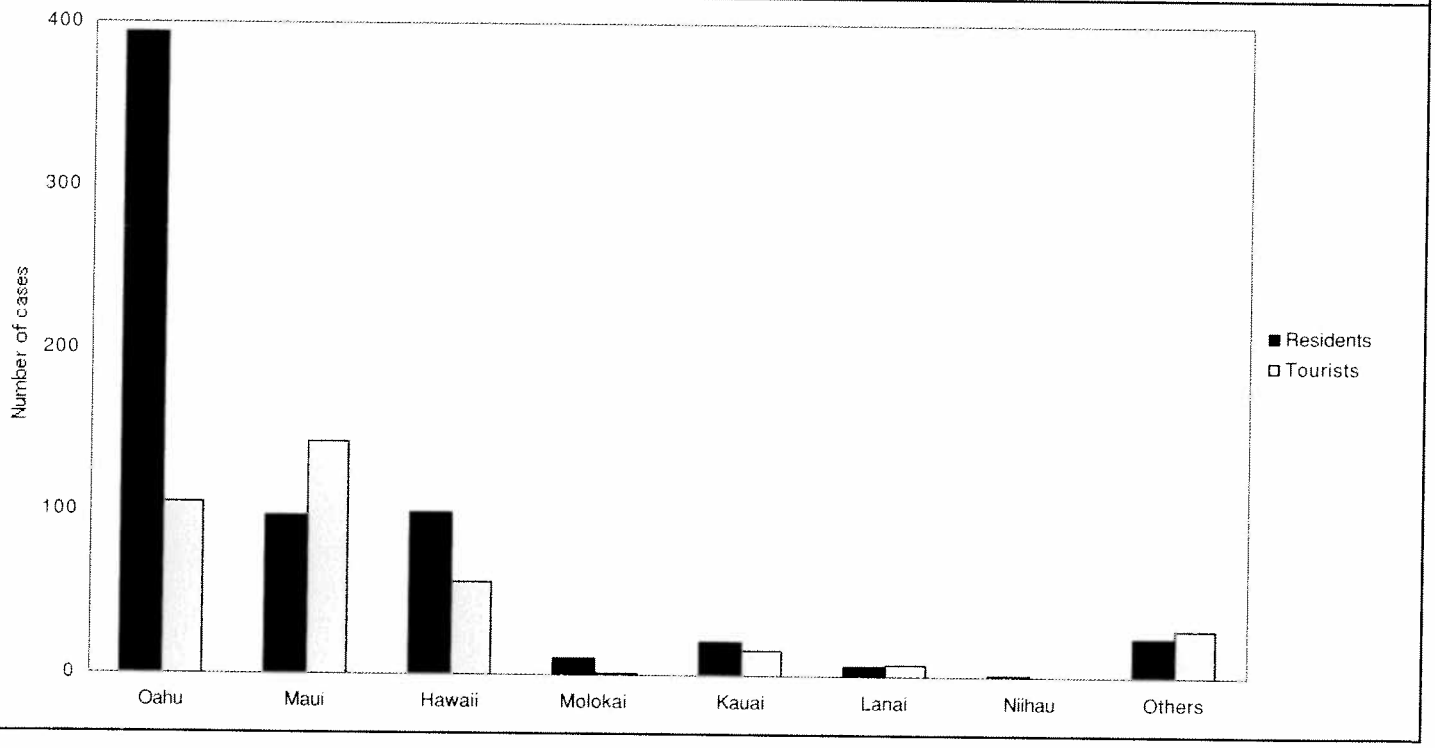

Table 1.—Comparison of injury type between residents and tourists (n=803)

	AGE		DCS		Total	
	Cases	%	**Cases**	%	**Cases**	%
Residents	46	8.3	505	91.7	551	100.0
Tourists	42	16.7*	210	83.3	252	100.0
Total	88	11.0	715	89.04	803	100.0

*$T=12.261>X^{2}_{(0.05),(1)=3.827}$

AGE : Arterial gas embolism

DCS : Decompression sickness

Table 2.—Comparison of gender of DCI cases between residents and tourists (n=803)

	Male		Female		Total	
	Cases	%	**Cases**	%	**Cases**	%
Residents	459	83.3	92	16.7	551	100.0
Tourists	154	61.1	98	38.9	252	100.0
Total	613	76.3	190	23.7	803	100.0

DCI : Decompression illness includes arterial gas embolism and decompression sickness.

Table 3.—Comparison of age groups of DCI cases between residents and tourists (n=784)

	20		21-40		41		Total	
	Cases	%	**Cases**	%	**Cases**	%	**Cases**	%
Residents	24	4.4	384	70.5	137	25.1	545	100.0
Tourists	24	9.6	162	65.1	63	25.3	249	100.0
Total	48	6.0	546	68.8	200	25.2	794	100.0

Until there's a cure, there's the American Diabetes Association.

Discussion

The Hyperbaric Treatment Center consistently ranks as the third most active treatment facility in the United States for diving injuries according to published statistics of the Divers Alert Network (DAN) located at Duke University for whom the HTC serves as the Pacific Regional Coordinator. Injury data from all reporting sites nationwide are compiled and analyzed yearly in an attempt to identify trends which may put divers at risk and to make recommendations for enhancing diving safety [5,6]. The Hyperbaric Treatment Center is the only facility providing treatment to non-military divers in the Hawaiian Islands. Thus most diving accidents that have occurred in Hawaii were treated there with the exception of military divers who were treated at Pearl Harbor, and a small number of divers who are known to have employed in-water recompression to treat themselves. Those two latter exceptions were not included in our data analysis. This study is limited by the fact that it focuses only on cases with injury that presented to the HTC. In order to determine incidence of injury, one must know the total number of dives undertaken by all divers yearly, and at the very least, in order to obtain a closer estimation of injury rate, one must know the total number of divers. This was an impossible task in either case, and thus we were circumscribed to present case-related data and analysis.

Since 1995, the total number of cases reported to DAN by the HTC has constituted 5% of the total number of cases reported nationwide [7]. Our data with respect to injury types, gender, and age distribution mirror the national trends [7]. Of special interest to us was the additional need to evaluate the relative rates of tourist injury and their locations within the state.

The overall trend in the number of cases treated at the HTC has decreased over the past 5 years. This may reflect several possibilities: fewer divers diving, safer diving practices being employed, or perhaps decreased visitation to the islands.

The age distribution in our cases was consistent with the national figures, but does show an increasing trend with older divers, which in all likelihood is constituted by aging "baby-boomers". An interesting observation was that tourists aged 20 years or less were injured at twice the rate of residents of the same age group. Due to insufficient data, we were unable to ascertain why this was the case. This could perhaps be attributed to a number of things not the least of which may be that many divers actually do their initial training here and therefore are less experienced and more susceptible to injury and/or that many tourists come as families and once here the lure of the ocean and the easy access to dive training promotes younger ages to take up scuba even though they may not be physically or mentally prepared to handle diving comfortably. Yet another concern develops when dive training is undertaken in a short period of time as is likely to be the case while on vacation, which does not allow adequate time to assimilate requisite diving knowledge [8,9].

Tourists also demonstrated higher rates of injuries in females, as well as in suffering an AGE, which is most often associated with buoyancy control problems or out of air ascents commonly seen in novice divers, and thus tends to support the previous comments regarding the younger aged cases. In an Australian study, tourists treated there were likely to dive only when they traveled and many had failed to maintain their diving skills [10]. At present, sports diving requirements do not compel divers to maintain their skills and knowledge. Moreover, diving certification cards have no expiration date. Diving after extended absence, unfamiliar dive sites, water conditions, or equipment, as well as language barriers in foreign visitors tend to increase diver stress and subsequent panic. The most common underlying cause of diving injury or death is panic [11].

With respect to site of injury, not unexpectedly most residents were injured on Oahu where the vast majority of the state's population resides. Interestingly, tourists were more apt to be injured while diving on Maui. This in large part is because diving sites there, particularly Molokini, are more pristine and offer visitors something more of a variety of diving experiences.

Conclusion

We have presented a descriptive epidemiological analysis of diving accidents treated at the Hyperbaric Treatment Center over the past 18 years. The Center continues to provide invaluable service to the state, its residents and visitors. Our patient population has been a microcosm of the nation with respect to trends in the parameters studied.

Acknowledgement

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Medical School Hotline

Pelvic Examination Teaching: Linking Medical Student Professionalism and Clinical Competence

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Introduction

The John A. Burns School of Medicine (JABSOM) Department of Obstetrics, Gynecology and Women's Health instituted a Professional Patient Program to teach medical students the breast and pelvic examination in 1973.[1] This third year medical student program is the longest standing program of its kind in the nation. Other medical schools have since realized the value of professional patients and have developed similar programs. This unique teaching program is currently engaged to teach the breast and pelvic examination to JABSOM medical students, Internal Medicine residents and researchers. Teaching medical students to approach such a sensitive portion of the complete physical examination as the pelvic examination with professionalism, empathy and sensitivity is a challenging endeavor.

The medical student often approaches the first pelvic examination experience with a high level of anxiety. At the beginning of each teaching session, the second and third year medical students write about their expectations and concerns. There are two strong consistencies in these responses; medical students are most concerned that they do not inadvertently cause any physical or emotional pain, or show disrespect to their patients during this exam. Building on those concerns, they expect the teaching sessions to provide them with a sense of competence in performing an accurate examination. They learn how to avoid creating any patient discomfort, disrespect or pain while performing the pelvic examination with clinical competency. The expectations in the two teaching sessions scheduled over their second and third academic years are often overwhelming, but it is precisely these anxieties that the Professional Patient Program seeks to address.

In a study comparing the traditional "gynecologist and clinic patient" method of teaching the pelvic examination to the "professional patient" method of teaching, medical students in the "professional patient" group were found to demonstrate significantly less anxiety than the "clinic patient" group.[2] This patient centered approach to teaching requires instruction in both the mechanics of performing the pelvic examination and the integration of patient centered professional skills. Defining professional competence is in itself problematic. Epstein defined professional competence as the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values and reflection in daily practice for the benefit of the individual and the community being served.[3] Although reliable teaching methods and assessment of basic skills and medical knowledge currently exist, the measure and teaching of professional behaviors and empathy has been lacking in the field. It is difficult to measure. In recent years, the use of standardized patients in United States medical school clerkships increased from 34.1% in 1993 to 50.4% in 1998. Despite this increase in the use of standardized patients, there are still many medical schools that fail to evaluate patient centered professional skills.[4] The JABSOM Obstetrics and Gynecology Professional Patient Program, in which the Professional Patients are trained to act as both teachers and evaluators, strives to teach and evaluate both the clinical skills and professional behavior necessary to conduct pelvic examinations.

Obstetrics and Gynecology Professional Patient Program

Professional Patients are selected through a rigorous interview process and are extremely dedicated individuals. The pool of applicants for this program is recruited initially through Patients already in the program and through the University of Hawaii. Final selection is based on a set of progressive interviews that determine whether a potential Patient candidate will work well within the program criteria. Although the Professional Patients come from a wide range of cultural and educational backgrounds, each individual has a strong sense of physical awareness of and comfort with her body. When this awareness is accompanied with strong teaching skills and the knowledge that her teaching is very important and valued by both the medical students and the school, she becomes a highly effective teaching Patient who can "teach from both ends of the table". When a woman is accepted into this program, a process of integration and training begins. The new Patient makes a commitment of at least one year. Despite this one year commitment to the program, 85% of Professional Patients have continued with the Obstetrics and Gynecology Professional Patient Program from two to twelve years. This has created a diversity in age, professional development and life experiences that has greatly benefited the program. Although Professional Patients are paid, they consistently express that they participate in the program because of a strong interest in Women's Health and a professional satisfaction in being able to contribute to the medical students' education. Performance in their dual roles as teacher and patient is evaluated by the students after each teaching session. These evaluations are reviewed with the Patient by the Program Coordinator.

Medical students at JABSOM participate in the Obstetrics and Gynecology Professional Patient Program as second year students and at the beginning of their third year Obstetrics and Gynecology clinical rotation. These teaching sessions are structurally similar and reinforce the specifics of their pelvic examination skills. Both the second and third year medical student teaching begin with a lecture and discussion session given by the Program Coordinator. Two of the Professional Patients demonstrate the specific professional and clinical skills necessary to perform the pelvic examination for the entire group of students, one acts as the "patient" and the other as the "physician". The medical student group then breaks into teams of two students and two Patients to perform the pelvic examination. During these sessions, immediate verbal feedback is given by the Patient to the student as to their professional and clinical skills. The students are encouraged to correct immediately their behavior and

perform the examination several times. At the end of their teaching session, a verbal assessment is given to the students by the Patient and a written assessment of their professional and clinical skills is reviewed by the supervising physician. At the conclusion of the teaching session, the students meet to discuss their experiences with the Program Coordinator and submit an anonymous written evaluation of their training experience.

Second Year Medical Student Program

The second year medical student pelvic examination teaching program sessions are coordinated with an anatomy laboratory session taught by the JABSOM Department of Anatomy*. Cadaver prosections demonstrating the female and male reproductive organs are reviewed prior to the pelvic examination teaching session. The integration of a reproductive anatomy laboratory session and pelvic examination teaching session expands the students' understanding of the pelvic examination. The anatomy lab is discussed at the beginning of the Professional Patient training session and a short pelvic examination videotape is viewed, followed by a twenty- to thirty-minute pelvic examination demonstration by two Professional Patients. The large student group then divide into teams of two medical students and two Professional Patients. The second year medical student spends about thirty minutes learning to perform the basic breast and pelvic examination and observing their fellow student performing the same examination.

Third Year Medical Student Program

Third year medical students receive their pelvic examination training at the beginning of their clinical Obstetrics and Gynecology rotation. Emphasis is on expanding clinical skills that include the Pap smear procedure and professional behavior. Each student spends up to an hour learning the breast and pelvic examination with Professional Patients. Role-playing is integrated into the session so that the Professional Patients can coach and advise on the use of particular words, phrases and approaches to the pelvic examination. Medical students are coached on professional appearance and demeanor. They practice their pelvic examination skills from "knocking on the door" and introducing themselves, explaining the pelvic examination, to the performance of the exam itself. Constant feedback is given to the student by the Professional Patient. The student has many opportunities to correct and improve on his or her clinical skills and professional behavior. The Pap smear procedure is also taught and these slides are reviewed by the JABSOM Department of Pathology**. The medical student is given written feedback on the adequacy or inadequacy of his or her Pap smear slide. Prior to seeing patients during their clinical Obstetrics and Gynecology rotation, each student has observed at least two professional patient pelvic examination demonstrations, observed two exams performed by his fellow students and performed at least two thorough pelvic examinations.

Medical Student Evaluation

The assessment of each medical student's performance is an integral part of the Professional Patient teaching program. These evaluations consist of immediate verbal feedback during the session, verbal feedback at the end of each pelvic examination teaching session followed by written evaluations. In addition, the student is provided a verbal evaluation of their clinical, behavioral and interpersonal skills by the Professional Patient. After the students are dismissed, Patients complete a written evaluation of each student that includes a checklist of those clinical skills and professional behavior steps performed adequately or inadequately. Narrative comments are added to elaborate on areas such as communication skills, appropriate professional behavior and respectful attitude. These evaluations are reviewed by the supervising physician and returned to the students.

Summary

The Professional Patient teaching program is an essential part of assuring competency in the performance of the pelvic examination and professional behaviors. Through a series of integrated teaching sessions from the first year reproductive anatomy laboratory, the second year basic clinical pelvic examination teaching program, to the third year teaching program, students perform at an enhanced level of clinical competency and professional behavior. A Professional Patient commented: "We create a safe environment where medical students not only learn the clinical portion of the exam, but also focus on the patient as the primary source of information on patient comfort. Students receive immediate feedback from us and have ample opportunity to ask questions about aspects of the clinical pelvic examination or doctor/patient communication skills. We guide them, teach them, and help them prepare for examinations with other patients who will not be as open or in tune with their bodies as we are."***

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Cancer Research Center Hotline

Laboratory Analysis of HER-2/*neu*: Search for the Optimal Testing Strategy

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Over the last decade increases in the understanding of human carcinogenesis have been remarkable. While this knowledge is far from complete, the identification of specific genetic and molecular events promises to radically alter the way cancers are treated by elucidating molecular targets for new pharmaceutical agents. A few such drugs have already been developed including Gleevec, targeting c-kit; Iressa, targeting epidermal growth factor receptor; and Herceptin, targeting the HER-2/*neu* (HER-2) protein. These agents show promise as primary treatment or as adjuvant therapy combined with standard treatments such as surgery, radiation therapy, chemotherapy and hormonal therapy. This new experience with "pharmacogenomics" has also brought new challenges for the diagnostic laboratory. The proper identification of patients who may benefit from these new drugs is critical. Equally important is identifying who is not a good candidate as these drugs may have serious side effects and are very expensive. This new developing pathology practice of identifying and characterizing therapeutic targets has been termed "pharmacopathology".[1] The current controversy surrounding the laboratory evaluation of HER-2 status is the prime example of this new dilemma in diagnostic pathology. It is worthwhile for pathologists and clinicians alike to examine this debate for it is a preview of what may well follow as more molecular based therapies advance through the clinical trial phase and into clinical practice. The HER-2 debate is an object lesson in why close interaction between the clinician and the pathologist is becoming more and more important. It is imperative that the pathologist becomes more familiar with the management implications of diagnostic tests. Likewise, clinicians must realize that there is more to pathologic evaluation than a hard copy result. Proper interpretation of pathologic results, whether they be from your local lab or data appearing in the peer-reviewed literature, requires an understanding of the testing process. The HER-2 story is a complex one that involves not only laboratory practice but also significant marketing and economical concerns. These "non-medical" forces must be understood as they clearly affect what appears in the peer-reviewed literature on this subject and directly shape marketing campaigns to clinicians and pathologists. In this commentary I will attempt to summarize the information, and misinformation, currently available and propose a rational approach to HER-2 testing.

The current debate focuses on what is the preferred method for HER-2 evaluation. While several methods have been employed since the discovery of the HER-2 gene and protein in 1985[2-4], the two clinically relevant methods are immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC is used to measure receptor protein expression and FISH is used to measure HER-2 gene copy number. The controversy centers around the reliability of IHC-based HER-2 testing and whether FISH should be the testing method of choice. To sort out this conundrum it is best to first review a few aspects of HER-2 biology, the laboratory issues in the development of anti-HER-2 therapy and the processes of immunohistochemistry and fluorescence in situ hybridization.

Overexpression of the HER-2/*neu* gene can be demonstrated in 20-30% of invasive breast cancers.[5,6] The gene is located on chromosome 17q and encodes a transmembrane tyrosine kinase receptor related to epidermal growth factor. In most, but not all, cases overexpression of the HER-2 protein (called p185) is associated with amplification of the HER-2 gene. The importance of HER-2 alterations is two-fold in that it has both prognostic and predictive value. Prognostically, tumors with overexpression or amplification are associated with shorter disease-free and overall survival while retrospective studies have shown that HER-2 alteration may be predictive of response to certain types of chemotherapy.[7] Most importantly, the HER-2 protein is the target of trastuzumab (Herceptin), the humanized monoclonal antibody now available for the treatment of breast cancer. Optimal use of this drug requires accurate determination of HER-2 status.

In 1993, as a result of clinical data from the Herceptin trial, it was apparent that a commercially available IHC test was necessary to determine patient selection for Herceptin. At that time, practical gene-based tests were not available. During the trial a combination of two antibodies called the "Clinical Trials Assay (CTA)" had been used to detect overexpression. The IHC staining was semi-quantitatively assessed on a 4-tiered scale (0, 1+, 2+, 3+) by evaluating the amount and intensity of cell membrane staining. Pre-clinical work suggested that Herceptin activity required a receptor density greater than 100,000 to 200,000 per cell. This roughly corresponded to an IHC score of at least 2+ by CTA so patients with 2+ or 3+ scores were considered candidates for Herceptin while those with scores of 0 or 1+ were considered non-overexpressed. The CTA assay was costly and difficult to perform making it an impractical test commercially. Genentech, the makers of Herceptin, granted Dako Corporation a license to develop an IHC kit that could be commercially used to detect HER-2 overexpression. The original tumor samples from the patients in the Herceptin trial had deteriorated so the newly developed antibody and testing protocol (HercepTest) along with the CTA were applied to a large set of tumors obtained from the National Cancer Institute. The tumor set was specifically chosen to have equal numbers of positive (2+, 3+) and negative (0, 1+) cases. This is a far more rigorous scenario than actual clinical practice where approximately 80% of cases will be clearly normal (0, 1+) or clearly overexpressed (3+). The comparison study showed a concordance between CTA and HercepTest of 79%. Based on this, the FDA unanimously approved HercepTest as the method for determining patient eligibility for Herceptin. The HercepTest procedure is more than just the polyclonal antibody (clone A0485). In an attempt to minimize variation from lab to lab the kit also includes all reagents along with a specific testing protocol and detailed interpretive guide.

Because most of the criticism of the IHC method of HER2 assessment is centered around the reported variability of the IHC method, a brief review of the IHC process is necessary. The IHC

method for identifying specific proteins in histologic preparations has been common in the pathology laboratory for over 20 years and is performed daily in most labs. The method consists of multiple steps, all of which can be modified by the laboratory to optimize the desired result. These processes include tissue fixation, antigen enhancement techniques, incubation times and conditions, dilution of the primary antibodies and detection methods (linking molecules and chromogens). In essentially all antibodies routinely used by pathologists the primary goal is to determine if a certain protein is present or not. For example, IHC stains for keratin may be used to determine if a tumor displays evidence of epithelial origin. The pathologist does not care *how much* keratin is present, just whether it is there or not. Because of this "yea or nay" approach procedures for specific IHC stains vary from lab to lab, depending on lab preference. Antibodies themselves vary in that different "clones" are available which may detect similar, but not identical, epitopes. No less than seven antibodies directed against various epitopes of the HER-2 protein are commercially available.[8,9] It is not surprising that interlaboratory variability results in this setting but with "qualitative" IHC this is not a major problem. The IHC determination of HER-2, however, is unlike any other IHC test. Because HER-2 is also present on normal breast epithelial cells it is necessary to quantitate the number of receptors present and establish a cut-off point above which "over-expression" is present. This concept of "quantitative" IHC is new for pathologists. While the HercepTest kit introduced the concept of quantitative IHC, it was also far more expensive for laboratories to utilize compared to other HER-2 antibodies. As a result, many laboratories altered the procedures, both in testing conditions and in the antibodies used. Many of these deviations formed the basis of HER-2 results reported in the literature and it is not surprising that variation resulted.

With this background on the development and variation in the laboratory methods of IHC we can look at the criticisms of this method of HER-2 assessment. A major factor adding to the intensity of the discussion was the availability of an alternative testing method, fluorescence in situ hybridization (FISH). Because of the stability of DNA, FISH testing could be performed on tumor samples previously tested by IHC and the results compared. In spite of what is implied in FISH marketing tactics, the procedure is not simple. It includes its own set of variables including tissue fixation, testing conditions, probe characteristics and interpretive criteria. In addition, FISH is significantly more expensive and performed by far fewer labs than IHC. This latter point is the primary reason that variability studies done to date have suggested FISH is more reproducible than IHC. As FISH testing becomes more widespread, interlaboratory variation will become more of a problem. When the IHC/FISH comparison studies were done, concerns quickly arose regarding the accuracy of IHC, and by implication, the reliability in patient selection for Herceptin therapy. This latter issue, that of patient selection, is especially important for Genentech, the manufacturer of Herceptin. If the test used to select the patients most likely to respond is flawed the perceived efficacy of the drug is at risk. As a result, Genentech has been active in the questioning of the IHC method and has been promoting FISH methodology.

The most commonly cited study by those advocating FISH over IHC for HER-2 testing is the report by Pauletti et al.[10] In that study 900 cases of invasive breast cancer diagnosed between 1987 and 1991 in South Australia were tested for HER-2 status by IHC and FISH with results compared with patient survival. Both methods were independent predictors of survival on multivariant analysis. By univariate analysis, there was a direct correlation between survival and gene copy number determined by FISH while that same relationship was only seen in the strongest staining IHC group (3+). This study has been put forth as evidence that FISH is the more accurate test. Keeping in mind the intricacies of IHC methodology discussed earlier, it is worthwhile taking a closer look at the Pauletti study. This re-analysis was well described by Yaziji and Gown and a few pertinent findings stated here.[11] The authors of the Pauletti study used the R60 polyclonal antibody which is not widely available and has been infrequently studied. They did not use antigen retrieval which is considered standard in most labs today. They utilized the peroxidase-antiperoxidase detection system which was common in the 80's and early 90's but has since been replaced by more sensitive methods such as avidin-biotin or streptavidin-biotin. These technical problems with the Pauletti study likely introduced both false positive and false negative IHC results leading to the suboptimal performance of their IHC assay. Another study raising concerns about the IHC method is the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-31 which looked at the benefit of adding Herceptin to chemotherapy.[12] Eligibility was based on HER-2 results from the accruing institutions and included cases that were either 3+ by HercepTest, showed strong membrane staining if other HER-2 antibodies were used, or gene amplification by FISH. Central HER-2 retesting was performed for the first 104 cases entered and showed that 18% of the community-based assays could not be confirmed by central HercepTest or FISH assay. The authors questioned the reliability of IHC performed in lower volume laboratories since repeat IHC and FISH testing at the central, large volume lab showed corcordance in 94% of cases.

A third example of problems with IHC can be found in the experience of the Breast Intergroup Trial N9831 which also is evaluating Herceptin in the adjuvant setting.[13] A secondary endpoint of the trial is to assess concordance between HercepTest and FISH at a central testing facility. Eligibility was the same as the NSABP B-31 trial. Of the first 119 patients entered, 110 had local IHC testing while only nine had local FISH assays. On central IHC repeat testing only 81 of the 110 (73%) showed 3+ staining with HercepTest. This again raised serious concerns about the accuracy of IHC, particularly when performed in lower volume community laboratories. What is not emphasized by those who cite this study as evidence of FISH superiority is that local vs. central FISH assays also showed poor concordance. Of the nine patients entered with local FISH testing showing gene amplification, only six (67%) were confirmed on central FISH testing. When both IHC and FISH were performed by the central lab there was 92% concordance. The 8% discordance consisted of cases that were 3+ by HercepTest but non-amplified by FISH, a consistent subgroup that will be mentioned later.

The publication of these studies and some others led to questioning of the reliability of IHC for determining HER-2 status. This effort has been supported by Genentech and those with interests in FISH technology. Subsequently many published reports have followed showing that IHC is, in fact, very reliable when strict adherence to testing and interpretive protocols are followed.[14,15] It has also been clear for some time that the "2+" IHC category should

not be considered "over-expressed" and requires additional testing. In spite of this fact, the proponents of FISH continue to cite studies that included 2+ reactions as "positive" as evidence of the shortcomings of IHC. An example of the excellent results that can be obtained when high quality IHC is performed can be seen in the data presented by Yaziji and Gown.[11] Among the 381 tumors negative for amplification by FISH, only six (1.6%) showed 2+ staining on IHC. Of the cases positive for overexpression on IHC (3+), 94% were amplified by FISH. This and many other studies published in the last 3-5 years as well as data from our own lab confirms that IHC, when well performed is highly accurate in determining HER-2 status.

As you can see from this discussion the large majority of the literature addressing the issue of IHC vs. FISH for HER-2 testing consists of comparison studies and retrospective studies looking at HER-2 as a prognostic factor. As mentioned previously, many of these studies are seriously flawed by variation in IHC testing practice and inconsistency in how results are reported. What has been lacking until recently is data showing the direct relationship between HER-2 testing methods and patient response to Herceptin. This important data is now starting to appear in the literature. In data submitted to the FDA from the Herceptin Clinical Trial (H0648g) significant improvement in time to progression was seen in patients receiving Heceptin plus chemotherapy compared with those receiving chemotherapy alone. This benefit was not only seen in patients who were IHC 3+/FISH+ but also in a subgroup of patients who were IHC 3+/FISH-, giving a false negative FISH rate of 13%.[16] In a study evaluating Herceptin as a single first-line agent in patients with metastatic breast cancer, 29 patients who were IHC 3+ responded to Herceptin. Twenty-seven patients with FISH positive tumors responded however 2 patients who were FISH negative (7%) also showed objective response.[17] Most recently, in a phase II monotherapy trial from Germany, clinical response to Herceptin was limited to those patients with IHC 3+ tumors. Most of these were also FISH positive but three patients who responded were FISH negative, a FISH false negative rate of 15%.[18] Clearly, the most recent and clinically relevant data shows that a strongly positive IHC test correlates best with patient response. This only makes sense given that the target of Herceptin is the p185 surface protein, the protein measured by IHC quantitative testing. In this sense FISH should be looked at as a "surrogate" test for Herceptin eligibility. It appears there is a small (7-15%) but consistent group of patients who are IHC+/FISH- that will respond to Herceptin. This may be due to chromosome 17 polysomy or low-level amplification with FISH HER-2 ratios between 1.0 and 2.0.

It seems then that when we look for the optimal testing method for HER-2 status we have come full circle. We began with IHC and now it is clear that IHC, indeed, is the best first-line test. What we have learned during the journey is that quality laboratory practice is more critical than the method itself. A laboratory that performs IHC in a sloppy fashion will likely perform FISH just as poorly. If a laboratory cannot ensure that the appropriate procedures are followed and that HER-2 results are continually monitored and data analyzed then samples should be referred to labs that have these procedures in place. The College of American Pathologists is currently structuring a HER-2 quality control program to help labs address this issue. While FISH is an alternative to IHC in first-line testing, a more appropriate role is in confirming borderline or "2+" IHC cases. This approach utilizing IHC as the initial test followed by reflex FISH testing for indeterminate cases has now been supported by many groups and is included in the recent National Comprehensive Cancer Network (NCCN) Guidelines.[16,19]

In our laboratory we have optimized the interpretation of HercepTest by applying digital computerized image analysis. The ACIS image analysis system (ChromaVision Medical Systems, San Juan Capistrano, CA) utilizes custom software to analyze HercepTest IHC stains. This technique is more accurate than manual scoring and improves reproducibility.[20,21] Automated IHC analysis will likely become more common as the area of pharmacopathology expands.[22] In conclusion, the saga of HER-2/neu testing is complex but necessary to understand for it is a vision of the future where multidisciplinary interaction, critical literature review, and bit of healthy skepticism are needed to determine the path to optimal patient care. While HER-2 testing will continue to evolve, current data indicates the optimal testing strategy should employ quality IHC with reflex FISH testing of indeterminate results.

For information on the Cancer Research Center of Hawaii, please visit www.crch.org.

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NHCOE Summer 2003 Conference..., continued from p. 162

population in Fiji by 40,000! **Richard Kasuya, MD, MSEd,** JABSOM Assistant Dean for Medical Education, completed the day with an interactive workshop on *Faculty Development: Creating and Delivering Effective Lectures: A Workshop for Clinician-Teachers.* **Dean Cadman** made opening comments at the dinner presentation and was followed by *Personal Reflections on Drs. Ozzie Bushnell and Charles Judd* by **Richard Marks,** Kalaupapa resident, **Gavan Dawes, PhD** historian and internationally reknowned author whose 700-page doctoral thesis Ozzie reviewed, **Kalani Brady, MD** Internist, and **Niall Scully, MD** thoracic surgeon innovator of numerous thoracic surgical procedures. Dr. Scully let Charlie speak to attendees directly by screening his 1982 video-interview by George H. Mills, MD.

The Sunday morning session was *A Tribute to Charlie Judd.* The first two presentations dealt with *Emerging Medical Concerns in Native Hawaiian Communities.* **Kelli-Ann Voloch, MD,**Waianae Coast Comprehensive Health Center pediatrician, noted in *Obesity in Native Hawaiian Children* that 26% of native Hawaiian children are overweight compared to 11% nationally. **Barry Carlton, MD,** Queen's Medical Center Chief of Psychiatry and JABSOM Vice-Chair of Clinical Services, in *Crystal Methamphetamine* described demographics and epidemiology of drug use here and said Hawaii is the crystal methamphetamine capital of the US with 38.1% of arrestees in Honolulu testing positive. Acute lead poisoning in habitues can result from contamination during drug production. The last three presentations of the morning addressed *Advances in Surgical Treatments for Diseases Affecting Our Communities.* **Brandt Lapschies, MD,** JABSOM Clinical Associate Professor, private practitioner and caregiver at Waianae Coast Comprehensive Health Center, enumerated *Surgical Interventions in the Treatment of Obesity.* He said the 43% prevalence of obesity among native Hawaiian adults and children far exceeds that of any other ethnic group here. **Elna Masuda, MD,** Straub Chief, Department of Vascular Surgery, in *Leg Ulcers and Vascular Disease in Paradise,* detailed risk factors for vascular disease in native Hawaiians and corrective surgical procedures. **Niall Scully, MD** concluded the Sunday session by analyzing his experience between 1996 and 2003 at Kohala's North Hawaii Community Hospital with *Surgical Techniques in the Treatment of Lung Cancer in Native Hawaiians.*

Director Young, his staffer Ruth Fujita, and your Associate Editor will, in the coming weeks and months, be working under the direction of our Editor to complete an *HMJ festschrift,* a commemorative special issue, honoring Charlie and Ozzie. We will clarion a call for papers shortly, and solicit personal anecdotes from people who knew either Dr. Judd or Dr. Bushnell. Towards the goal of garnering funding and other support for establishing the *Charles S. Judd, MD and OA Bushnell, PhD Endowed Chair of Hawaiian Medical History* at JABSOM, we say *I mua!*

News and Notes Henry N. Yokoyama MD

Potpourri I

Side Effects: Two doctors got lost in a hot air balloon. They saw someone on the ground. They shouted to the man on the ground. "Can you tell us where we are?" The man looked up, thought for a while... "You're about 50 feet off the ground and you're located directly south east of where I'm standing."

One of the doctors in the balloon turned to the other and said: "He must be a neurologist." "How can you tell?" "Well, he thought about the problem carefully... his answer was remarkably correct, but it didn't help us one bit."

Dr. Howard Bennet (STITCHES Nov 2002)

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Not So Religious: In matters of arithmatic down under it's "maths" but in Canada it's "math"...

This gave rise to an interesting situation... One afternoon in Emergency when an elderly couple presented with the complaint that the wife had lost her memory over the preceding week...

After some inquiry, I embarked upon a mini mental assessment... The poor lady was, however, all at sea when it came to serial sevens...

Feeling sorry for her embarrassment, I commented, "I guess you weren't very good at maths when you were young?" There was a pause, then both partners chimed in together, "Oh, no, we're not Catholics... We're Protestants!

Dr. T.R. Atkin (STITCHES Jan 2002)

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Medical Tid Bits

A Smart Woman Would Wear Coffee as a Perfume: A study by scientists at Mass General found that low doses of caffeine given to mice, effected the A2A receptors located on the neural cells next to those that degenerated in Parkinson's Disease... Harvard researchers in an epidemiological study found that men who drank 4 to 5 cups of coffee had less risk of Parkinson's Diseases.

The Weathervane... Russell T. Stodd MD

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Beyond Cholesterol: (Researchers now believe that inflammation and cholesterol work together to increase the risk of heart disease.) Too much fat in the blood builds up as plaques in the heart vessel walls. Its presence triggers the inflammation alarm; attacking immune cells such as monocytes mature into macrophages which engulf the fatty plaques... The immune activity elicits the liver to produce CRP which engulf the fatty plaques... As immune cells pile onto the plaque, it becomes unstable and ruptures... Debris from the lesion can cause a blood clot or trigger a heart attack.

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Hypertensive Hype: A study by the National Heart, Blood and Lung Institute (NHLBI) showed that mild diuretics are the least expensive means of treating most cases of high blood pressure and the most effective as well.

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Folic Acid: There is some evidence that FOLIC ACID reduces the risk of heart disease, but it is best known for its role in preventing spina bifida and other birth defects...

Now comes word that the vitamin may help ward off the ravages of Alzheimer's Disease... Researchers at Boston University and Tufts University found that subjects with levels of homocysteine were twice as likely to develop Alzheimer's... One of the easiest ways to lower homocysteine levels is to consume plenty of folic acid.

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The Japanese eat little fat and suffer fewer heart attacks than the British and Americans... The French eat a lot of fat and also suffer fewer heart attacks than the British or Americans... The Italians drink a lot of red wine and also suffer fewer heart attacks than the British or Americans... Conclusion: "**Eat and drink what you like... Speaking English is apparently what kills you**..."

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The New Carcinogenes: The US government added steroidal estrogen (like the kind used in hormone replacement and birth control pills) to its list of "known human carcinogens— a/c increased risk of endometrial and breast cancer.

Classified Notices

To place a classified notice:

HMA members.–Please send a signed and typewritten ad to the HMA office. As a benefit of membership, HMA members may place a complimentary one-time classified ad in HMJ as space is available.

Nonmembers.–Please call 536-7702 for a nonmember form. Rates are $1.50 a word with a minimum of 20 words or $30. Not commissionable. Payment must accompany written order.

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The Weathervane Russell T. Stodd MD

It's Not The Heat, It's The Validity.
In Singapore, authorities have converted a thermal imaging camera used by the military into a screening device for the deadly virus, severe acute respiratory syndrome (SARS). Now more countries are joining in this effort to ferret out travelers with fevers. The infra-red camera can detect one degree or more above 98.6 F. without touching the person. The camera does not measure the temperature, but has been calibrated to produce a red image of the feverish individual. The passenger showing red is directed to a nursing station where a nurse in gown and mask, rechecks the temperature. The individual is made to sit down for 30 minutes, and if the fever remains above 100.4 F. the traveler is referred to a hospital dedicated to caring for SARS patients. The checks are fast, non-intrusive, and people are usually oblivious. Some say "thank you" after being informed they were checked and found normal.

Beauty Is Only Sin Deep.
Having spent thousands of dollars for a face lift, eyelid lift, fat-sucking-tummy tuck, butt lift, and botox in the brow, now what does a lady do about those hands - - wrinkled, droopy, liver-spotted, gross dilated veins - a dead giveaway of her age? Fear not! Here comes da plastic guy (again)! First, some fat is sucked off the thighs or other "problem areas," and injected into those saggy pockets of skin, then zap the wrinkles with special lasers that stimulate collagen, collapse the bulging veins with saline solutions, and finally peel away the discoloration and sun spots with the laser. Voila! Madame is back to age 39. Well, 45 maybe?

Cooperation Is Everything. Freckles Would Make A Nice Tan If They Got Together.
As a political power in matters of medical liability at our legislature, the Hawaii Medical Association is pretty puny, no matter how vocal and righteous we are. What is needed in Hawaii is what was recently accomplished in the state of Idaho. A broad-based and powerful coalition was formed of small business, product manufacturers, big business, county governments, the Idaho Medical Association, store owners, and many others, all united to establish a liability law which effectively squashed the trial attorneys. Similar to Idaho, here in Hawaii we have hundreds of organizations and individuals just as angry as doctors are at trial lawyers and the abuse of the liability process. In Idaho, every politician was contacted by an influential person in his/her district to emphasize why tort reform was necessary. The politicians listened. It took time, money, organization, and a willingness to cooperate, and it worked.

We Have Confused The Free With The Free And Easy.
Not satisfied with the great boost in income resulting from direct to consumer advertising DTC, General Electric and GE Medical Systems in conjunction with NBC, have created the Patient Channel. Available only by satellite, the Patient Channel is wired directly into 550 hospitals and medical facilities across the country, and serves as a marketing tool for the pharmaceutical industry. They plan to boost that number to 1100 medical units by September. *Commercial Alert*, a not-for-profit organization based in Portland, Oregon, sent a letter (co-signed by 37 doctors) to the CEOs of all hospitals and hospital chains of 2000 beds or more, urging them to say no to this crass, ad delivery system. It is increasingly apparent that the pharmaceutical people have no shame.

Is Anyone Interested In Sweetness And Light?
A study of an exciting new polyvalent vaccine *Prevnar* made by Wyeth was conducted by the CDC and reported in the New England Journal of Medicine. The study encompassed a seven state network that monitored the cases of pneumococcal disease in a population of 16 million people. The findings were so dramatic that public health recommendations are that all children should be so immunized. The vaccine is effective against meningitis, blood infections, and pneumonia, and showed a 69% reduction in serious diseases caused by pneumococcus in children less than two years old. An interesting corollary was that older siblings, parents and other adults in the household benefitted as well. Disease rates for adults 20 to 39 years old, dropped 32% while those over age 65 showed a decrease of 18%, even though they had not received the vaccine. There is a drawback, of course. The price is $61/shot and four injections are required. Still, considering the cost of treating such illnesses, it is well worth the cost. Many pediatricians and family physicians are already making the vaccine routine.

The Best Thing To Eat On A Diet Is — Less.
Dr. Robert Atkins, the weight conscious doctor who conceived the Atkins Diet, a controversial low- carbohydrate weight loss program, died recently. He slipped on ice, struck his head and died of a brain injury. Rather sad that he did not live to see his diet findings published in the New England Journal of Medicine (NEJM May 22). Researchers had several cautions and were careful not to endorse the diet, but their studies indicated a short-term benefit. In a study of 63 obese men and women, the Atkins patients lost on average, 15 pounds after six months. The group on the low-fat, high carb diet lost only 6.9 pounds in the same period. In a similar six month study at Philadelphia Veterans Affairs Medical Center of 132 obese patients, the Atkins cohort dropped 13 pounds compared to 4 pounds for the low-fat group. Moreover, the Atkins diet showed a greater reduction in triglycerides, and despite a higher saturated fat intake, investigators, found no significant increase in "bad cholesterol" levels.

We Ought Not To Do Wrong When Other People Are Looking.
In a study reported in the *Journal of Medical Ethics*, researchers wanted to attempt a measurement of ethics of medical students at Dundee University in Scotland, The study included 461 students who were asked if they would consider writing "Nervous system examination – normal" in a patient presentation without having performed the procedure. A mere 2% of first-year students said yes to the question, but 45% of their older counterparts in years 2 and 3 indicated they would consider it, and 54% of fourth-year people said yes to the hypothetical scenario. This is preposterous!! Why aren't these "yes" students in law school?

There Is Certainly No Exact Standard Of Quality.
The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) stated that beginning in 2006, inspections would be unannounced, and rather than a three year cycle, they would drop in every two to four years. This is good. Now medical organizations won't spend months in worrisome preparation for JCAHO's paper shuffling nuisance pretense at quality analysis. Hospitals will have 45 days to correct any problems noted by the nitpickers. Hospital quality is extremely important, but JCAHO has failed to be that vehicle.

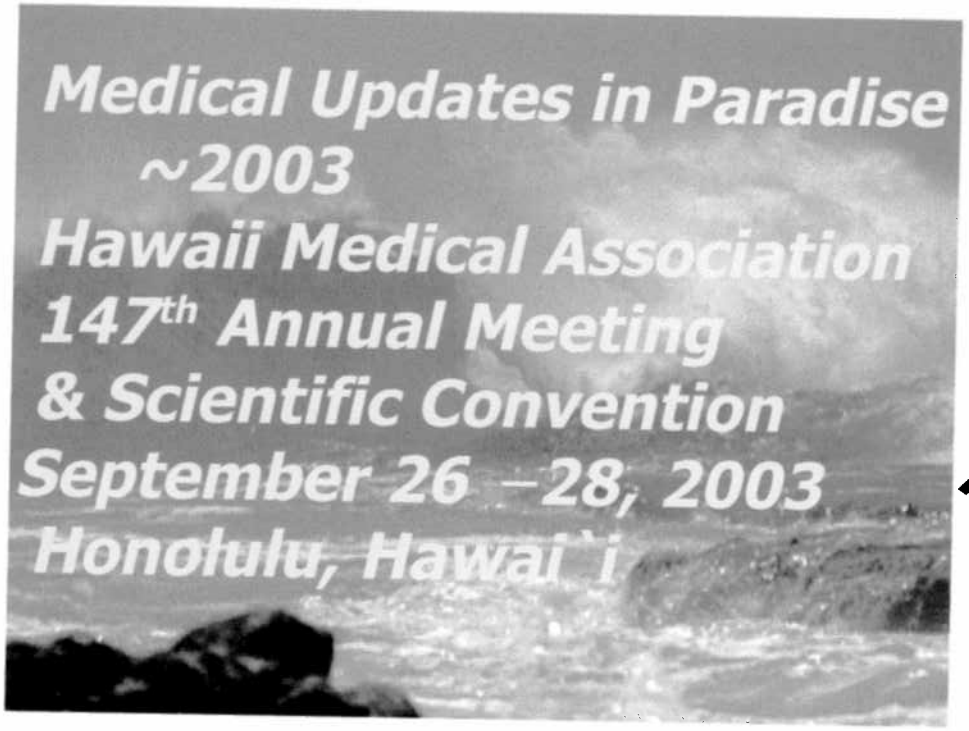
I'm Out Of My Mind, But Feel Free To Leave A Message.
You may have read some of these gems before. They come from medical testimony doctors offered in court and are recorded in the *Journal of Court Reporting*. To quote: "By the time he was admitted, his rapid heart had stopped and he was feeling better." "Patient states there is a burning pain in his penis, which goes to his feet." "On the second day the knee was better and on the third day it had completely disappeared." "Patient has been depressed ever since she began seeing me in 1983." "Patient refused autopsy." "Patient has left his white blood cells at another hospital." And finally, "She slipped on the ice and apparently her legs went in separate directions in early December."

ADDENDA
- 25% of the oxygen in your vascular system, is used by the brain.
- Hello, fat America! For flight calculation purposes, the FAA is recommending that average passenger summer weight be increased 10 lbs to 190 lbs. and winter weight be increased to 195 lbs.
- In one or two weeks, Girl Scouts sell 10% of all the cookies sold annually in the nation.
- Eight nickels = two paradigms. 100 Senators = not one decision.

Aloha and keep the faith —rts■

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

Aloha



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Hawaii 2003

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In uncertain times, seek the high ground

TIMES ARE TOUGH IN PROFESSIONAL LIABILITY INSURANCE—again. Insurers are restricting coverage, leaving the market and some have disappeared. MIEC was founded by doctors in similar turmoil in 1975.

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