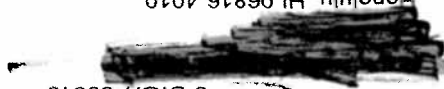


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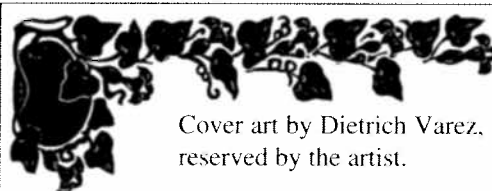
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Lamalama

Lamalama refers to fishing at night by torchlight.



Norman Goldstein MD
Editor, Hawaii Medical Journal

Tobacco Isolated as a Cause of Skin Aging
Still Another Reason to Quit Smoking!

Thirty years ago, while attending a Board meeting of the American Cancer Society with a dozen or so attendees, there were three ashtrays at the conference table, almost filled to capacity with cigarette butts before the meeting was over.

Today, thanks to the efforts of the American Cancer Society, the American Heart Association, the National Cancer Institutes and the US Public Health Service, smoking has been drastically reduced. Because of heavy taxes on cigarettes, the high cost of smoking has also reduced usage, but this is still not enough. Forty-eight million Americans, 24% of the adult US population continue to smoke.¹

The October 3rd issue of the *New England Journal of Medicine* had two special articles and an editorial on smoking. In the editorial, "Conflicting Dispatches from the Tobacco Wars," Steven A. Schroeder noted prevention and cessation as the principal strategies in the battle against tobacco use. Prevention is aimed primarily at children and youth. These strategies include anti-tobacco education, counter-marketing, guidance on ways to resist pressures to experiment with tobacco, increased taxes on tobacco products, advertising, and marketing restrictions, placement of warning labels on products and advertisements, enforcement of laws governing the minimal age to purchase, and efforts to influence social norms. Equally important are efforts to help existing smokers quit. When they stop smoking, benefits are achieved immediately: by the well-known lowered risk of heart disease, alleviation of chronic bronchitis, reduction in the threat of fire injury, and over time, diminished risk of cancer, chronic pulmonary disease and other diseases.²

In the Schroeder editorial, and the article by Gross et al, the authors explain that total spending on tobacco control accounts for only 12% of the tobacco settlement dollars hard won in all 50 states.

"It has been four years since the tobacco industry reached settlement agreements with all 50 states, and it has been suggested that the settlement is not living up to its promise. Despite the newly imposed marketing restrictions, the 24% increase in expenditures by the tobacco industry in the year after the settlement (for a total of \$8.42 billion) was the highest ever. There has been no significant decrease in youth-directed magazine advertisements. Paradoxically, the tobacco industry continues to enjoy increasing revenues: although the price of cigarettes has increased by up to 50% in the two years after the settlement, cigarette sales decreased only by about 10% in the same period."³

States spending ranged from a low of 10 cents per capita in Pennsylvania to \$15.47 in Maine. Hawaii's expenditure per capita was \$10.82 in 2001. This was above the actual amount recommended by the CDC of \$9.08. Hawaii received \$35,800,000 in the 2001 settlement.⁴

Hawaii's Department of Health Tobacco Prevention and Education Program should be congratulated for its efforts. Julian Lipshe, MPH, CHES, a public health educator, and his associates have material available to help our patients. He may be contacted at 808-586-4662 or via e-mail to jdlipshe@mail.health.state.hi.us.

The American College of Obstetrics and Gynecology produced an excellent educational brochure dealing with smoking and women's health.⁵ In addition to cancer, coronary artery disease and pulmonary disease are the less known but equally important effects on menopause, reproduction, ovulatory dysfunction, tubal dysfunction, spontaneous abortion, and pregnancy.

So how do dermatologists⁶ get involved in the campaign to stop smoking? Research has shown that smoking increases the risk of squamous cell carcinoma of the lips and oral cavity. Cigarettes also have been implicated in the development of melanoma. Nicotine diminishes blood flow and reduces oxygen supply to the skin. The well-known "smoker's face," with deep wrinkles and discoloration, and the "crow's feet" wrinkles at the lateral edges of the eye, the sallow pale skin around the eyelids are also associated with smoking. Now, we have demonstrated proof that smoking causes wrinkles and accelerates aging of the skin of both sexes. Cornelis Kennedy, M.D., MPH, in the Department of Leiden University Medical Center, the Netherlands, studied almost 1,000 smokers. As expected, increasing age and sun exposure were significant factors in skin aging. Both men and women smokers had more elastosis and telangiectasis than non-smokers. Telangiectasis, however, was higher in men than women. The authors of the study could not explain this, but as Kennedy said at the recent Society of Investigational Dermatology meeting, "in Western society, looks are very important and millions (perhaps billions, Ed.) of dollars are spent on looking good. Quitting smoking may help you look better; plus it's cheaper."⁷

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Notes from the HMA Annual Meeting 2002 Scientific Session

Russell T. Stodd MD

The 146th annual meeting of the Hawaii Medical Association was held at the Orchid at Mauna Lani on the big island the week-end of October 4th to 7th. Along with the House of Delegates meeting, attendees had the benefit of a large display of exhibits from a multitude of medical companies and agencies which serve Hawaii's physicians. If there is a single message in this report it is that too many of Hawaii's physicians are missing one of the least expensive, yet superlative educational programs, an escape week-end at a gorgeous location (with special kamaaina rates), a great group of medical exhibitors, and all in conjunction with the annual HMA House of Delegates meeting. The program committee chaired by Rhoads E. Stevens MD, again did a magnificent job and deserves accolades. All I can say is **WAKE UP, HAWAII DOCS**, it is time to support your HMA and this excellent annual meeting. It is carefully crafted, and a terrific educational and social experience.

On Friday morning, our highly esteemed leader of the Department of Health, Bruce Anderson PhD, gave a comprehensive overview of steps taken to combat terrorism. He also reported on the rapid and expansive coverage of the dengue fever outbreak on Maui. This was followed with a brilliant, enthralling discussion of the history and current laws of anti-trust, especially in relation to organized medicine. Two legal experts, Stephen Foreman, JD, PhD, MPA, Director, Pennsylvania Medical Society Health Services Research Institute, and Thomas J. Campbell, JD, Dean HAAS School of Business, University of California, presented information never previously offered to Hawaii's physicians, and provided remarkable insight into how to best approach anti-trust. Tim Norbeck, EVP of the Connecticut Medical Society, went over details of their medical society law-suit against third parties which has been joined by the Hawaii Medical Association against HMSA. Altogether, an engrossing and informative morning session.

The second day was directed at primary care physicians with pure medical science. Thomas File, MD Professor of Internal Medicine at Northeastern Ohio University College of Medicine, discussed new pathogens, pneumococcus and adeno-viruses. He also presented guidelines for lab studies and care, especially hospitalizations vs. outpatient care. Patrick Joseph, MD, Clinical Professor of Medicine infectious disease, University of California at San Francisco, gave an excellent, but alarming analysis of HIV and AIDS. The prevalence of AIDS in the "developing nations" in the future appears uncontrollable. He also presented interesting data of 10 years experience with HIV, and discussed viral load and viral fitness in relation to therapy. The morning session included a careful study of how to manage the diabetic foot, offered by H. Gunner Deery, II, MD, infectious disease specialist at Northern Michigan Hospital.

The illustrations were excellent with great emphasis on weight bearing and regular examination of the feet, because so many diabetics develop lower extremity anesthesia.

The second half of the morning session was divided among three orthopedic surgeons. Thomas J. Kane, III, MD, of Queens Medical Center gave an extensive analysis of hip injuries and disorders. Sherwin S.W. Ho, MD, Clinical Professor of Surgery at the University of Chicago presented the management of shoulder problems. He pointed out that a careful history is the key to appropriate diagnosis. It was an interesting program of atraumatic and traumatic shoulder damage. Last on the orthopedic agenda was a witty and captivating discussion of knee problems presented by Allen B. Richardson MD, Professor of Orthopedic Surgery at JBSCM. The subject wasn't funny, as he went over patellofemoral pain, meniscal tears, and repute of the anterior cruciate ligament, but the presentation was marvelous. Dr. Richardson kept the audience amused and always interested.

The last session on Sunday AM, dealt with what is happening in anesthesiology, critical care and resuscitation. Robert Bonham, MD, Director of the Emergency Department at Waianae Coast Health Center, dealt with use of the puff and pump - the newest guidelines for CPR and emergency cardiovascular resuscitation. Michael J. Murray, MD, PhD, Mayo Clinic, Jacksonville, Florida, titled his program, "Something Old, Something New, Something Borrowed, Something Blew: New Therapies in Critical Care Medicine." The old is Vasopressin (ADH) for use in septic shock. The new is treating septic shock with a dose of activated protein C (drotrecogin alfa), expensive but justified in certain cases. The something borrowed is the appropriate use of erythropoietin in treating anemia in the ICU. Something blew referred to the treatment of acute respiratory distress syndrome (ARDS) where it is now known that positive end-expiratory pressure (PEEP) does not cause an increase in survival. Moreover, some iatrogenic factors actually increased mortality due to injury to pulmonary tissue. William J. Jazzei, MD, Clinical Professor of Anesthesiology at UCSD Medical Center, San Diego, California, gave an excellent discussion of what is new in and out of the operating room. Short term, safe, general anesthesia is in order for many cases. Day surgery has become an increasing area of care.

In summary, this encapsulated discussion of the educational program is profoundly feeble in describing the excellent material offered to those who took advantage of this educational experience. In abiding optimism, I sincerely hope the value of the HMA annual meeting will become obvious to more of Hawaii's health professionals.

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

A Descriptive Epidemiologic Study of HIV-Infected Individuals in Hawaii: Report of the Hawaii Sero-Positivity and Medical Management Database (HSPAMM)

Dominic C. Chow MD, MPH, Suzanne M. Richmond-Crum BA, Sheri M. Shimizu BS, Joey Kohatsu BS, Scott A. Souza PharmD, Andy Grandinetti PhD, Kevin K. Urada PhD, and Cecilia Shikuma MD

Abstract

This is a retrospective study of the HSPAMM database evaluating differences in clinical, laboratory, HIV-risk factors and demographic characteristics with respect to gender and ethnicity. There were no significant differences comparing gender, and Hawaiians and non-Hawaiians with respect to developing a CD4 count <200 cells/mm³. HSPAMM contains information on a large number of HIV-infected Asians/Pacific Islanders.

Introduction

The State of Hawaii Department of Health estimates that there are between 2,300 to 3,200 individuals living in Hawaii who are infected with the human immunodeficiency virus (HIV). Since 1989, the Hawaii Sero-Positivity and Medical Management (HSPAMM) program has provided a means to monitor HIV infection within the state. The purpose of HSPAMM is to (1) encourage those who are HIV infected or at risk for HIV infection to consult a physician to prevent disease progression, (2) provide ongoing clinical assistance to participants, (3) classify groups of infected people by specific criteria so that they may participate in clinical trials and research, and (4) maintain anonymous demographic, clinical and laboratory records about participants. The HSPAMM program provides semi-annual visits for all its participants with their own primary care physicians. An HSPAMM visit consists of a patient questionnaire, a health provider questionnaire, a general physical examination, and collection of laboratory samples. We report the descriptive epidemiological analysis of the HSPAMM database covering April 1989 to July 2001. The purpose of the study was to define whether differences exist in clinical, laboratory findings, HIV-risk factors and demographic characteristics with respect to gender and ethnicity.

Methods

An overview of how data are obtained through HSPAMM is displayed in Figure 1. The patient questionnaire is self-administered and consists of 43 questions, which include the patient's demographics, risk factors, medical history, medication use, and signs and symptoms. Ethnicity was defined as Caucasian, African American, Hispanic, American Indian, Asian/Pacific Islanders, and other ethnicities. Asian/Pacific Islanders were further classified as Chinese, Japanese, Filipino, Hawaiian/Part Hawaiian (individuals who report having any Hawaiian heritage), and other Asians not of Hawaiian descent. The questionnaire given at each HSPAMM visit is repeated and intended to capture changes within the interim period. The physician medical history includes the patient's clinical signs, symptoms, health status, onset of opportunistic infections, and development of HIV associated diseases. The general physical examination, included in the physician medical history section, records the patient's vital signs and review of all organ systems. The laboratory portion of the HSPAMM visit includes CD4/CD8+ counts, HIV viral load, chemistry panel (electrolytes and liver function tests), complete blood count with white blood count differential, Papanicolaou testing for women, and hepatitis B and C serologies. All data collected from participants are recorded under an individualized code number, in which only the treating clinician knows the name of the participant, so as to insure confidentiality.

This is a retrospective descriptive epidemiologic study of HSPAMM participants from April 1989 to July 2001. During this period there were minor modifications to the questionnaires and laboratory testing. These modifications were made in response to the increased awareness of the natural progression of HIV disease, availability of anti-retroviral medications and other medications used to treat HIV complications, and improved laboratory technology. There were a total of 722 variables collected from the patient questionnaire, physician medical history, and laboratory tests.

The data were analyzed using SPSS version 10 (SPSS Inc., Chicago, IL) and STATA version 7 (StataCorp, College Station, TX). Descriptive epidemiological analyses were performed on all variables. Group differences within gender, ethnic, and risk factors were compared using one-way analysis of variance. Significant differences across these groups were indicated by the F-test. The

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source of inter-group differences was determined by using a two-sided t-test. An alpha level less than 0.05 was considered significant.

An unadjusted Cox proportional hazards model was used to compare the rate of developing a CD4 count <200 cells/mm³ among men and women who had an enrollment CD4 count ≥ 200 cells/mm³. Potential risk factors for developing a CD4 count < 200 cells/mm³ was examined by using multivariate proportional hazards models adjusted for ethnicity, enrollment CD4 count, and history of anti-retroviral therapy. Similarly, a Cox proportional hazards model was used to compare Hawaiians and non-Hawaiians in developing a CD4 count < 200 cells/mm³, and adjusted for enrollment CD4 count and history of anti-retroviral therapy. The risk of developing a CD4 count of <200 cells/mm³ was used since this is an acquired immunodeficiency syndrome (AIDS) defining event. Other AIDS defining events were not consistently captured by HSPAMM.

Results

From April 1989 to July 2001 there have been 2,460 HSPAMM participants resulting in 12,832 visits. Incomplete visits, defined as having one or more missing questionnaires (patient questionnaire, physician medical history, and laboratory panel) in a visit, were detected in 758 (5.9%) visits. Of all visits, there were 698 missing patient questionnaires, 698 missing physician medical histories, and 491 missing laboratory sections. The median follow-up was four 6-month interval visits, with a mean follow-up of six 6-month interval visits. Of all participants, 19% made a single visit, 12% made 2 visits, 10% made 3 visits, and 59% made 4 or more follow-up visits. There were no differences between length of participation and gender. African Americans had a substantially shorter length of participation compared to other ethnic groups (4.8 visits compared to 6.3 visits). Length of participation increased with increasing income and among the men having sex with men (MSM) population. The average length of HIV infection prior to enrolling in HSPAMM was 3.8 years (median of 2.0 years). Annual enrollment by ethnicity is displayed in Figure 2.

From the patient questionnaire database, 2221 (90.7%) were male, 196 (8.0%) were female, and 33 (1.3%) had no response. The age of these participants at their initial visit ranged from 18.0 to 71.1 years (mean age = 37.2 years; median age = 36.2 years; mode age = 37.0 years). Among participants over the past two years, participants over the age of 50 made up 27.9% of the current database. The demographic characteristics of the HSPAMM database is shown in Table 1. The distribution of participants residing on each island is shown in Figure 3.

The length of residence in Hawaii at first enrollment ranged from <1 year to 68 years (mean = 11.3 years; median = 5.0 years; mode less than 1 year). At first enrollment, participant who moved to Hawaii within 1 year tended to be younger (median age of 37 and mode age of 24) compared to participants who had resided here for > 5 years (median age of 40 and mode age of 43). Risk factors for HIV disease are displayed in Table 1. Of all participants reporting injection drug use (IDU) on their initial HSPAMM visit, 50.1% (173) reported sharing needles on a regular basis with an average of 2.3 individuals (median 2.0). The average of HSPAMM visits found 22.4% of participants report using nitrate inhalants, 49.4% marijuana, 17.8% inhaled cocaine, 9.3% methamphetamines, 3.2% IV cocaine, and 1.8% IV heroin. The facilities where participants

received their initial HIV positive test were sexually transmitted disease (STD) clinics (39.1%), physician offices (31.1%), other health clinics / hospitals (24.1%), blood banks (1.9%), and no response (3.8%).

At enrollment, 1456 of all participants reported an income less than \$20,000 (63.1%). The number of men and women according to stratified incomes at enrollment are displayed in Table 1. For participants with two or more follow-up visits, reported income on subsequent visits did not change significantly from that reported at enrollment (mean change in individual income stratification was +0.7 with a standard deviation of ± 1.1). At the initial visit, the housing situation was as follows: 12.3% owned their own home, 57.2% rented, 11.8% were in temporary housing, 2.7% were homeless, and 0.6% were in shelters (15.4% did not respond). Of the 66 homeless individuals, 40.0% (26) went on to find housing situations while the rest continued to be homeless.

The average CD4 count at enrollment was 357 cells/mm³ for men (median 330) and 399 cells/mm³ for women (median 350). Of 2,460 participants, 1,657 participants had an enrollment CD4 count ≥ 200 cells/mm³. There were no significant difference in the cumulative proportion of men and women in developing a CD4 count of <200 cells/mm³ (Hazard Ratio of 0.98, 95% CI [0.69, 1.39], $P=0.91$). This finding was unchanged even after adjustment for ethnicity, enrollment CD4 count and history of anti-retroviral therapy use (Hazard Ratio of 1.07, 95% CI [0.74, 1.55], $P=0.70$) (Figure 4).

The ethnic distribution according to stratified CD4 counts at enrollment is displayed in Table 2. There were minimal differences in stratified CD4 counts between ethnic groups except between Hawaiians and non-Hawaiians. There was a significant difference of 40 cells/mm³ in mean CD4 counts between Hawaiians and non-Hawaiians at enrollment. Hawaiians had a median enrollment CD4 count of 80 cells/mm³ lower than non-Hawaiians, with largest difference between Hawaiians and Caucasians of 128 cells/mm³. However, no difference in proportional hazards was seen between Hawaiians and non-Hawaiians in developing a CD4 count <200 cells/mm³ (Hazard Ratio of 1.20, 95% CI [0.86, 1.68], $P=0.30$), even after adjustment for enrollment CD4 count and history of anti-retroviral therapy (Hazard Ratio of 1.02, 95% CI [0.72, 1.45], $P=0.91$).

Discussion

Since 1989, HSPAMM has provided the State of Hawaii Department of Health insight into the demographics and health behavior of this unique group of HIV-infected individuals. Although not all HIV-infected individuals living in the state participate in HSPAMM, this group constitutes the largest HIV database in Hawaii. The database is unique in that it allows us to examine the demographic, clinical and laboratory status of a large HIV-infected population living in the State. Although the median follow-up is four 6-month interval visits, 20% of participants have been followed over 5 years. Enrollment of participants was initially high at about 300 per year in early 1990's and has subsequently declined. Recent years have seen HSPAMM enrollment steady at 110-150 per year (although follow-up and utilization have increased steadily over time). This trend is proportional to the estimated incidence of HIV infection in Hawaii.¹ Possible etiologies for this decline are fewer HSPAMM enrollment, HIV conversion or HIV-infected individuals moving to the state.

Figure 1.— Overview of the HSPAMM visit

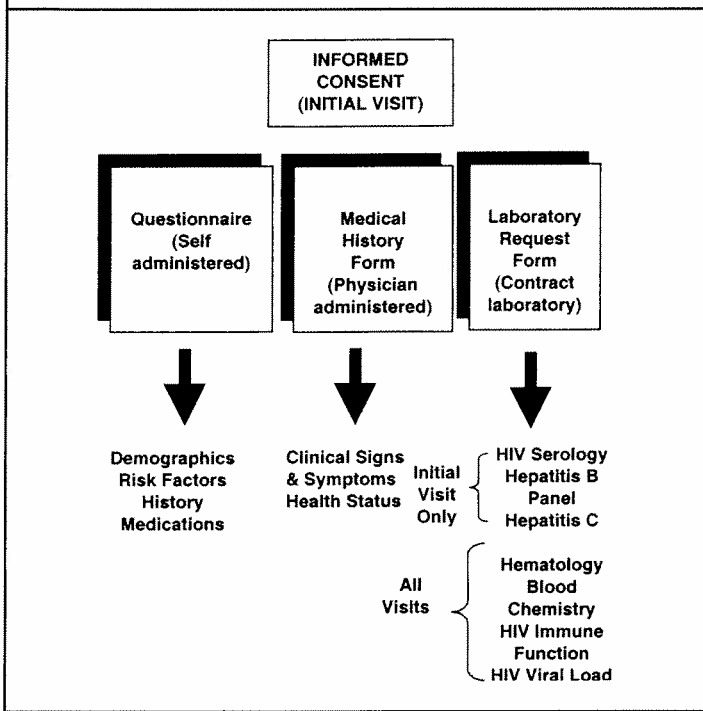


Figure 3.— Distribution of HSPAMM participants living in Hawaii

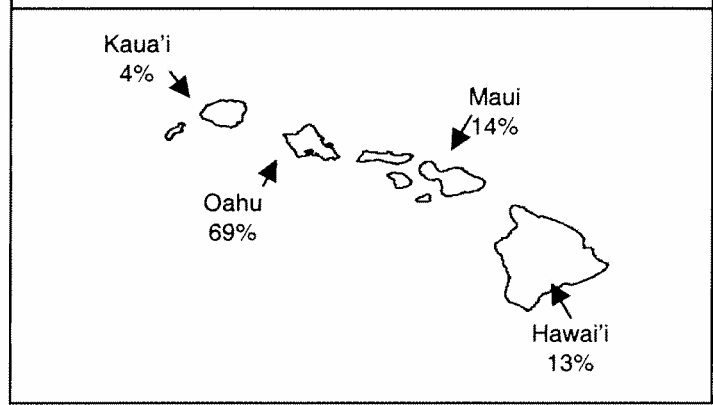


Figure 4.— Cumulative proportional of HSPAMM participants remaining free of developing a CD4 count < 200 cells/mm³ according to gender, adjusted for ethnicity, enrollment CD4 count, and history of anti-retroviral therapy

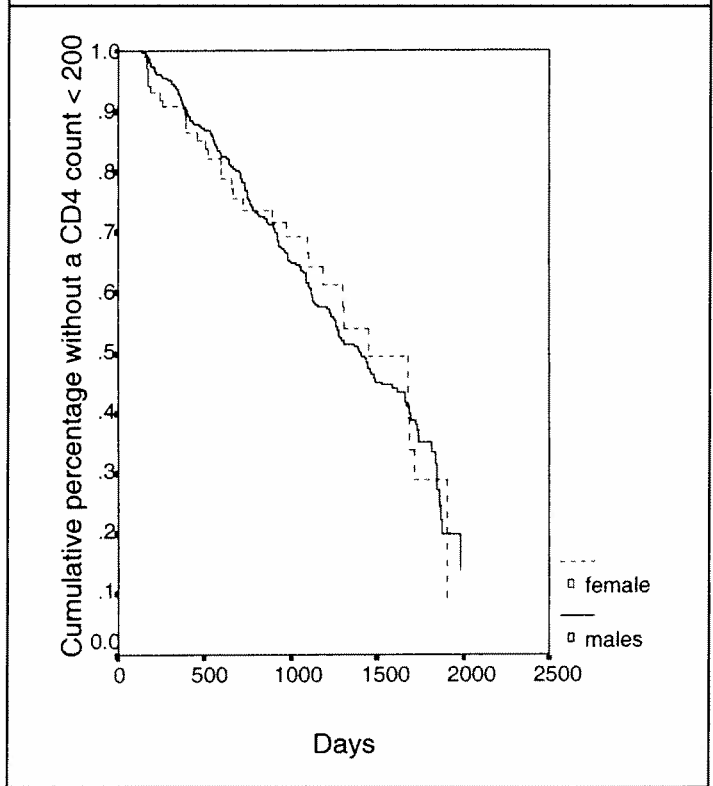
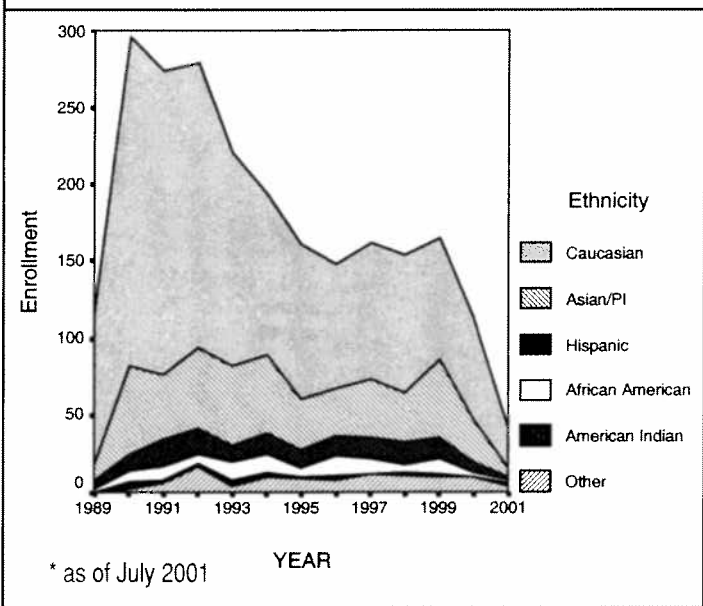


Figure 2.— Annual HSPAMM enrollment by ethnicity*



Although Hawaii is composed of a wide ethnic diversity, Caucasian males are disproportionately infected with HIV compared to other groups. The 2000 Census shows that of the 1,211,537 people living in the state, 41.6% are Asian (503,868), 24.3% are Caucasian (294,102), 9.4% are Hawaiian/Pacific Islander (113,539), 1.8% are African Americans (22,003), and 21.4% are Mixed Non-Hawaiians (259,343).² The number of Caucasians is disproportionately infected when compared to other ethnic groups living in Hawaii. The large number of Asian/ Pacific Islanders contained in this database makes this one of the largest database of HIV infected Asian/ Pacific

Islanders in the country. Asian/ Pacific Islanders make up 20.7% of the HSPAMM database compared to less than 1% of all case surveys in the national AIDS Surveillance database.³ The Asian HSPAMM participants are similar to national AIDS surveillance demographics in that the majority of participants are MSM (70% compared to 79% nationally).⁴

A large proportion of younger participants were found to have recently moved to Hawaii at enrollment. This migration to the State may be secondary to the better health coverage, the HIV Drug Assistance Program, and environmental/social atmosphere in Ha-

Table 1.— Demographic characteristics of HSPAMM participants

	Male	%	Female	%
Total	2224	92%	196	8%
Active Participants	761	89%	94	11%
Ethnicity				
African American	92	4%	9	4%
American Indian/ Alaskan Native	26	1%	2	1%
Asian/ Pacific Islander	425	19%	76	39%
Caucasian	1422	64%	84	44%
Hispanic	146	7%	12	6%
Other	110	5%	13	5%
Asian / Pacific Islanders				
Hawaiian/ Part Hawaiian	216		39	
Filipino	51		10	
Japanese	56		9	
Chinese	51		6	
Other Asian	51		12	
Risk Factors				
Men who have sex with men (MSM)	1694	77%	-	-
Injecting drug use (IDU)	82	4%	7	4%
MSM/IDU	187	8%	-	-
Heterosexual Contact	90	4%	120	60%
Blood/ blood products	6	(<1%)	9	5%
Other	162	7%	60	31%
Per Capita Income (\$)				
<10,000	854	40.2%	109	60.9%
10,000 - 19,999	458	20.6%	32	16.3%
20,000 - 29,999	296	13.3%	19	9.7%
30,000 - 39,999	192	8.6%	9	4.6%
40,000 - 49,999	106	4.8%	5	2.6%
50,000 +	217	9.8%	5	2.6%
Length of Residency				
< 1 year	528	23.8%	40	20.4%
1-5 years	597	26.9%	30	15.3%
6-10 years	294	13.2%	25	12.8%
10+ years	733	33.0%	93	47.4%
No response	69	3.1%	8	4.1%

Table 2.— Ethnic distribution according to stratified CD4 counts at enrollment

	CD4 Count (cells/mm ³)					
	≤ 50	51- 100	101- 200	201- 350	351- 500	>500
American Indian/ Alaskan Native	2	1	3	12	5	8
Asian/ Pacific Islander	60	45	81	114	75	102
African American	15	5	8	17	24	25
Caucasian	138	81	171	335	301	411
Hispanic	20	9	16	33	31	41
Other	16	9	21	36	26	31
Asian / Pacific Islanders						
Hawaiian/ Part Hawaiian	39	26	57	60	48	62
Filipino	11	3	5	13	13	13
Japanese	7	4	13	21	15	18
Chinese	3	2	6	13	5	3
Other Asian	16	3	6	21	9	17

waii compared to many parts of the country. Interestingly, seven physicians were responsible for seeing over 50% of HSPAMM visits. These 7 physicians are all known members of an association called the Community Consortium of AIDS Physicians Hawaii, a physician group that was formed with the purpose of improving HIV health care, research and awareness in the State.

The HSPAMM database consisted of older participants compared to the national average.⁵ Participants greater than the age of 50 make up 25.8% of all active participants. Butt AA, et al. report that HIV infected individuals with an age greater than or equal to 60 years was associated with shorter survival compared to HIV non-infected individuals.⁶ The health and resource needs of this population can also be expected to change as more infected individuals enter their golden years, and increasing emphasis may need to be directed towards health issues focusing on cardiovascular disease, HIV lipodystrophy, osteoporosis, and dyslipidemia.

HSPAMM includes HIV-infected individuals with and without a prior diagnosis of AIDS. The treatment of HIV disease is comparable to that seen nationally. There were 234 HSPAMM participants who transitioned from monotherapy or no anti-retroviral therapy to highly active anti-retroviral therapy (transition period occurring between 1995-1996). Results are similar to the Multicenter AIDS Cohort Study (MACS), in that the use of highly active anti-retroviral therapy (HAART) dramatically increased CD4 counts.⁷

Among men, MSM constituted the majority of HSPAMM participants (69%), slightly higher than that seen nationally (54%).⁵ Women made up 8.0 percentage of the database, much less than seen nationally (32%).⁵ The prevalence of HIV infection in women is unknown since HIV infection is not a reportable disease. The etiology of this gender disparity in HSPAMM is not known, but may suggest cultural and social barriers faced by infected women. There were socioeconomic differences between men and women. Women reported a lower education status (40% having attended college compared to 64% in men) and lower household income compared to men. However, the women participants in HSPAMM had comparable immunologic status to male participants. The women had a higher enrollment CD4 count. As seen in Figure 4, there was no significant difference in the cumulative proportion of men and women in developing a CD4 count of <200 cells/mm³, even after adjustment for ethnicity, enrollment CD4 count and history of anti-retroviral therapy use.

Hawaiians comprise 10% of the entire database and are the largest group secondary to Caucasians. Although no difference in proportional hazards was seen between Hawaiians and non-Hawaiians in developing a CD4 count <200 cells/mm³, the enrollment median and mean CD4 counts of Hawaiians were lower than that of non-Hawaiians, especially Caucasians. These differences persist with respect to visit sequences. The median and mean CD4 counts of Hawaiians appear parallel to counts seen in non-Hawaiians at each sequence. This difference was no longer seen after Hawaiians were stratified to enrollment CD4 counts. This may suggest that although Hawaiians respond to anti-retroviral therapy similarly to other ethnic groups, they seek medical attention for their HIV infection later than the other groups. Cultural, socioeconomics and access to care issues will need to be addressed in future studies.

Limitations of this retrospective study of the HSPAMM database are mainly from the construction of the database. The database is one

that is anonymous. Therefore, validation of data collected is difficult to perform and linkage to vital statistics unfeasible. Participants who drop out of HSPAMM are also difficult to locate. Controls were not intended and therefore results of this database are descriptive and hypothesis generating. The anonymous nature of the program allows for the possible duplication of participants, although procedures are in place to prevent duplication.

There are two major sources of bias which preclude generalization to the HIV-infected population at large. The first is that the cohort is self-selected. Participation is voluntary and there are many potential barriers to patient enrollment: denial, economic and cultural factors, geographic isolation, and some physician aversion to paper work. The second source of bias is that a large portion of the first year's enrollment included only MSM from a previous cohort established in 1985 called the Hawaii Men's Study.⁸

Describing representative populations such as HSPAMM helps prioritize and efficiently use human and fiscal resources for disease control and prevention purposes. Flexibility in modification and additions to the questionnaire, and clinical and laboratory database can assist administrators and health providers in asking pertinent health care questions for the future. In addition, HSPAMM provides necessary services and information to the large proportion of HIV infected individuals living in Hawaii.

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Therapy with Hypertonic Saline in Combination with Anti-Convulsants for Hyponatremia-Induced Seizure: A Case Report and Review of the Literature

Kristi S.M. Youn MSII and Jinichi Tokeshi MD

Abstract

Seizures are an uncommon but serious complication of hyponatremia which can lead to permanent brain damage and even death.^{1,2} It is recommended that patients with hyponatremic-induced seizures be treated with 3% hypertonic saline, however, a rapid rate of correction may result in central pontine myelinolysis (CPM), a severe neurological disorder characterized by mutism, dysarthria, spastic quadriparesis, and pseudobulbar palsy.² The patient in this case developed a hyponatremia-induced generalized tonic-clonic seizure which was aborted by rapid therapy with diazepam, followed by hypertonic saline and phenytoin. Subsequent replacement of hypertonic saline with normal saline and salt tabs in combination with phenytoin allowed gradual correction of serum sodium without any subsequent seizures or neurological complications.

Introduction

Hyponatremia is defined as serum sodium less than 137 mEq/L.¹ It is a frequent problem, especially in the elderly, affecting as many as 7% of healthy elderly persons.¹ Early signs of hyponatremia include: apathy, weakness, cramps, anorexia, nausea, vomiting, and headache which occur at levels of 125 mEq/L or less.^{1,2,5,7} Advanced manifestations include impaired response to verbal and painful stimuli, hallucinations, and urinary incontinence.⁷ Other serious complications are hyper/hypothermia, central diabetes insipidus, pulmonary edema, respiratory arrest, coma, seizures, permanent brain damage, and death from increased intracranial pressure or brain herniation.^{2,5,6,8} Most brain damage is associated with untreated hyponatremic encephalopathy in a limited number of clinical settings: postoperative state, polydipsia-hyponatremia syndrome, pharmacologic agents (analgesics, antidepressants, antineoplastics, diuretics, hypnotics, oral hypoglycemic agents, narcotics, sedatives, and tranquilizers), congestive heart failure, and AIDS.⁶

Studies show that 3-10% of patients with serum sodium levels below 130 mEq/L have seizures,^{3,4} particularly when serum sodium is lower than 115 mEq/L or there is a rapid decrease in serum sodium

concentration (less than 12 hrs⁹).⁷ Other factors that may lower the seizure threshold are electrolyte and glucose imbalance, ischemic encephalopathy, medications, and medication withdrawal.⁷

Symptomatic hyponatremia is a medical emergency since even small increases in brain volume (5%) can lead to substantial morbidity (4-15%)^{4,5,6} and mortality.^{5,6} Records show that correction by water restriction alone results in unacceptable morbidity and mortality,⁶ and treatment with hypertonic saline is associated with survival and recovery in symptomatic patients.^{5,6}

This report describes the case of a patient who had a hyponatremia-induced generalized tonic-clonic seizure and recovered without any subsequent seizures or neurological complications after treatment with diazepam, hypertonic saline, and phenytoin.

Case Report

A 69-year-old, Japanese female with a history of hypertension and sialadenitis treated with methylprednisolone (2 sets of 4 mg titrating dose) was seen in the office for routine evaluation and found to have a serum sodium of 121 mEq/L. Later that day, she felt "jittery" and nauseated. Methylprednisolone was discontinued due to her nausea. The following day, the day of admission, she vomited twice. She drank 4 large glasses of water after vomiting the first time. That night in the emergency room, she presented with nausea, vomiting, polydipsia, and "jitters". Her sodium measured 108 mEq/L. She subsequently had a witnessed generalized tonic-clonic seizure with cyanosis and was immediately given 5mg of diazepam IV, followed by infusion of 3% hypertonic saline at 25 ml/hr. The entire seizure lasted approximately 3 minutes. Phenytoin load of 750 mg IV at a rate of 40 mg/min was then given with a maintenance dose of 250 mg IV qd.

On physical exam, the patient was fatigued, yet able to respond to spoken words and follow commands. She did not recall having a seizure. Blood pressure was 120/60 mmHg, pulse 68/min, respirations 21/min and temperature 96.5 F. Skin had reduced turgor. Pupils were equal and reactive to light and extraocular movements were intact. There were no intranasal lesions, no mucosal irregularities or irritation of the oral cavity. Facial movements were symmetrical. A 3cm mobile, firm, tender, right submandibular mass was noted. Lung exam revealed few crackles bilaterally. Trace edema was noted in her extremities. On neurological exam, patient was alert and oriented to person and time. She performed well on the mini-mental status exam except for serial sevens. Cranial nerves II-

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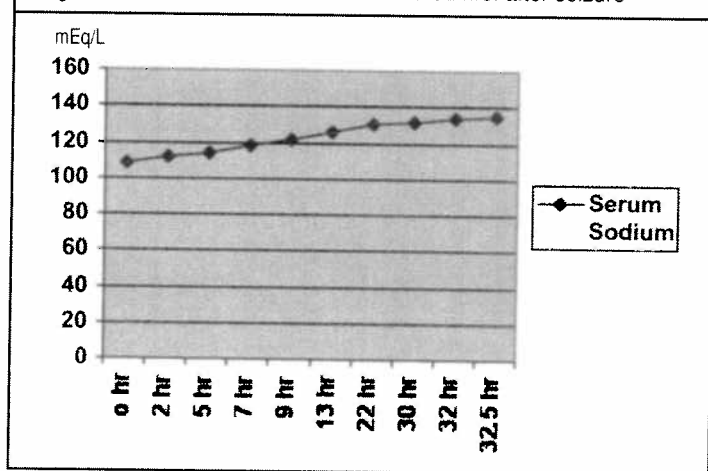
XII were intact. Muscle size, tone, and strength were normal and symmetrical. Babinski signs were observed bilaterally. Reflexes were normal. Touch sensation was also normal.

Laboratory values obtained included serum glucose 126 mg/dL, sodium 108 mEq/L, potassium 4 mEq/L, chloride 78 mEq/L, BUN 5 mg/dL, creatinine 0.4 mg/dL, osmolality 234. Urine osmolality 374 mOsmol/kg and sodium 79 mg/dL. TSH 1.69 μ U/ml, free T4 1.50 mg/dL. Serum cortisol 17.6 μ g/dL and 27.2 μ g/dL. WBC 13.8, Hgb 13.6, Hct 39.6, Plt 323. EKG showed prolonged QT intervals of 448 mili seconds and a U wave. CXR was normal. CT scan without contrast was negative for any intracranial process, although it showed an enhancing mass involving the right submandibular gland measuring 3x4x4 cm with areas of multi-lobulation.

The patient was admitted to ICU and sodium levels were checked every two hours. After two hours, her sodium rose to 112 mEq/L at which time the hypertonic saline was discontinued. Her intravenous infusion was replaced with normal saline IV at a rate of 150 ml/hr and salt tabs 1g po tid. Her serum sodium gradually increased to 130 mEq/L at 22 hours post-seizure (figure 1).

The following day she was transferred to the Progressive Care Unit, the salt tabs were discontinued and phenytoin was changed to 100 mg po tid. The patient remained stable and her sodium levels remained in the 130-136 mEq/L range over the next week. The day before discharge, she underwent right submandibular gland excision, which revealed a hemorrhagic ulcer with acute and chronic cellulitis, microabscesses, necrotizing sialadenitis, and reactive lymphadenitis without atypia or malignancy. On the day of discharge, the patient was stable, without neurological sequelae and sodium was 130 mEq/L. On follow-up exam, there was no evidence of any neurologic abnormalities.

Figure 1.— Serum Sodium Levels from 0-32 hrs. after seizure



Discussion

In this case, the patient experienced nausea and vomiting at sodium levels of 121 mEq/L as well as a seizure and pulmonary edema at a sodium level of 108 mEq/L. The cause of her hyponatremia was unknown. Although hyponatremia and seizure are not well-known side effects of methylprednisolone⁷, it was the primary suspect in this patient's case since the patient does not have any history of hyponatremia, epilepsy, or any of the risk factors for lowering the seizure threshold.

Current treatment recommendations for symptomatic hyponatremia include close monitoring, preferably in ICU,^{6,10} and correction

with 3% hypertonic saline and intravenous furosemide to raise sodium at a rate of 0.6-2 mEq/L/hr.^{1,5,6,10} During therapy, electrolytes should be checked every two hours, until the patient is neurologically stable.⁶ Patients with seizures require immediate anticonvulsant-drug therapy and adequate ventilation.⁵ If the patient continues to have seizures after anticonvulsant therapy, it is recommended that the sodium be raised by 4-5 mEq/L over the first hour or until seizure activity has ceased.⁶ A rapid increase of 3-7 mEq/L is enough to stop seizures induced by hyponatremia⁵, however, too rapid of a correction can lead to CPM. Guidelines for discontinuing hypertonic saline include a sodium increase of 20 mEq/L or sodium levels of 120-125 mEq/L.^{2,6} The patient's serum sodium measured 121 mEq/L less than 48 hours prior to admission, therefore, it was thought the symptoms were due to acute hyponatremia. Due to the urgent nature of the situation, hypertonic saline was infused at 25 ml/hr. Four hours later, the patient's serum sodium increased by 4 mEq and without further seizures, therefore the patient was felt to be stable and the hypertonic saline infusion was discontinued to prevent rapid correction. However, the serum sodium continued to rise and exceeded the recommended rate of correction.

Controversy remains over the rate of correction. However, most authorities agree that sodium levels should not be elevated by more than 8-12 mEq/L during any 24 hr period.^{1,2,4,5,6} Some studies show that increases of more than 12 mEq/L in 24 hrs were too rapid and resulted in CPM.^{2,10} Other studies show CPM only develops when 1) a patient is inadvertently made hyponatremic during therapy, 2) sodium levels increase by 25 mEq/L in the first 24-48 hrs, 3) the patient suffers a hypoxic event, or 4) has severe liver disease.^{2,5,6,10} It is also recommended that serum sodium not be corrected to eunatremic or hypertremic levels.⁶

Conclusion

Hyponatremia-induced seizures are a rare but serious condition that may result in permanent brain damage and death either as a primary cause or as a complication of therapy. In symptomatic patients, correction with hypertonic sodium chloride should be prompt, but strictly controlled for avoidance of neurological complications. Immediate administration of anticonvulsant drugs diazepam and phenytoin allowed gradual correction of hyponatremia and prevention of myelinolysis.

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Medical School Hotline

Role of the Library and Librarians in Medical Education at the John A. Burns School of Medicine

Virginia M. Tanji MSLS, MEd
Librarian

An informal poll of medical students indicated that they consider the library resources central to their learning process, especially with the problem based learning curriculum. They acquire skills that they will use during their clerkships as they strive to keep up with changes in medical practice throughout their careers. Marshall et al found that students in a problem based learning program tended to use the library more frequently, for longer periods of time and used library resources for a greater proportion of their study materials.¹

A JABSOM's student remarked:

"...the librarian can have a fairly substantial role in general medical education, especially in a curriculum like ours where the basic reading is left to students to discover. For me, librarians provide a great service in helping to develop research ideas and in literature searches for research projects, mainly in helping navigate the often confusing information sources available, both in the physical library and on the internet."

Librarians play a visible role in answering reference questions, providing workshops on searching the literature, and introducing students to the range of resources available. They also play a critical behind the scenes role in selecting and acquiring resources and making them accessible to their clientele. These roles continue, but technology has changed the way that library resources are made available and used. A critical part of the role of medical librarians is the teaching of information retrieval skills to medical students.

In 1989, MEDLINE was available for searches in the libraries via CD-ROM programs or dial-up modem through Grateful Med, a menu driven program that did not allow interactive searching (i.e. users received immediate feedback regarding their searches). This is taken for granted today but was a novelty in 1989. Few medical students had email accounts and students were just beginning to use the CD-ROM programs for searching MEDLINE. Students were being taught to search the journal literature with Index Medicus with heavy reliance on books and journals in the library.

Today, students have a small reference library available to them through databases such as *MDConsult*, *StatRef*, and *Scientific American Medicine*, plus a host of clinical journals via OVID. These resources are available 24 hours a day/7 days a week through Hawaii Medical Library and Hamilton Library.

This range of resources, print and electronic, is introduced to the students at the beginning of their studies through lecture and workshops conducted by the librarians at Hawaii Medical Library and JABSOM Library Resource Center (formerly the School of Public Health Library). The JABSOM problem-based learning curriculum makes effective use of library resources (teaching and references services) that are a "must" for students.

The librarians, as resource persons, are available for students. Students come in to look for epidemiologic data regarding a given

condition, or they might want to know the best treatment options related to the psychological aspects associated with a specific disease condition. These questions evolve into informal teaching opportunities as the librarians model searching behaviors that the student can use in the future. The librarians conduct workshops that deal with searching for the best "evidence" in the practice of medicine. These are skills that they will need as they practice in the community.

In their less visible role, librarians work behind the scenes to develop services that might best meet the need of the users. This includes selecting databases, journal titles, books, negotiating electronic licenses, and creating library web pages to make titles accessible within and without the library. There is the constant vigilance and troubleshooting required to make access seamless. Publishers and other providers are continually modifying their systems that cause links on the library's web pages not to work. A whole new layer of tasks have evolved around the electronic resources in addition to the printed journals and books.

The need for medical students to learn information retrieval skills has been recognized for many years² but the expansion in technology and information makes efficient use of these resources paramount. Years ago an officer of the Hawaii Medical Association, when asked for his support regarding continuing educating credits for a MEDLINE searching workshop, commented that learning to search the MEDLINE database should be thought of by physicians as a tool to be added to their armamentarium, like using a stethoscope or running and interpreting an EKG. Recently the "better_health Delphi Study" of the American Association of Medical Colleges, examined the views of the future by deans of medical schools, CEOs of teaching hospitals, and directors of medical libraries regarding the future of health care. They rated highly the statements that by 2010, "all current biomedical and clinical journals are available in digital format" and "information management skills will be assessed as a routine component of clinical skills."³

This is a period of transition in the role of the library in medical education. Much of the latest and best clinical information is available on the desktop via the library. The library and librarians play a key role in the effectiveness of physicians.

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Cancer Research Center Hotline

Gynecologic Cancers

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Introduction

Tremendous advances are being made in the treatment of gynecologic cancers today. Some of these advances are being made right here in Hawaii. Gynecologic cancer, including ovarian, fallopian tube, primary peritoneal, cervical, vaginal, vulvar, endometrial, uterine sarcoma, and gestational trophoblastic disease strike more than 100,000 women a year in the United States resulting in tens of thousands of potentially preventable deaths. Exciting advances are occurring in cancer surgery, chemotherapy, radiotherapy, and the biological understanding of these cancers. This paper will review the basics of the major cancers: ovarian, cervical, and endometrial and touch on some exciting new advances.

Ovarian Cancer

Ovarian carcinoma is the second most common gynecologic malignancy in the United States. Each year, ovarian cancer strikes 26,000 women killing an estimated 14,000. This represents 55% of all deaths from gynecologic cancers, making ovarian cancer the most lethal gynecologic malignancy.

Epithelial ovarian tumors originate from coelomic epithelial cells that cover the ovary and account for approximately 65% of all ovarian cancers. Germ cell cancers and stromal cell cancers account for the remaining proportion of ovarian cancer. Epithelial tumors may be benign, "borderline" (low malignant potential), or malignant. The invasive epithelial cancers have a peak age incidence between 55 and 65, although patients can be diagnosed from 10 to 100.

When considering ovarian cancer, most people refer to the most common and most deadly type: epithelial. Two other epithelial ovarian-like cancers are fallopian tube and primary peritoneal, which do not originate in the ovary, but are biologically virtually identical.

Ovarian cancer frequently involves the omentum and/or retroperitoneal lymph nodes with pleural effusions or parenchymal liver metastasis. Approximately 70% of women present with advanced Stage III and IV disease and have a median survival rate of less than 25%. The overall survival for all epithelial ovarian cancer is 50%.

The survival rate for local, regional, and distant stage disease is similar between ovarian carcinoma and breast carcinoma. However, the overall survival for women with ovarian cancer is substantially less than for those women with breast cancer due to the preponder-

ance of late stage ovarian cancers. Unlike mammography in breast cancer, there is no effective screening test for ovarian cancer. Combine this with few specific early symptoms, and it is understandable why most women with ovarian cancer are diagnosed with Stage III and IV disease.

Only a few factors have been linked to an increased risk for the development of ovarian cancer. These include increasing age, family history of breast or ovarian cancer, personal history of colon or breast cancer, and nulliparity. Really, we don't know what causes this disease. On the other hand, the risk of developing ovarian cancer is reduced by 60% with five years of oral contraceptive use. The protective effect of oral contraceptive use appears to be long-term. In addition, pregnancy also reduces ovarian cancer risk, as does tubal ligation and breast-feeding.

For women in the general population without a family history of ovarian cancer, the lifetime risk is about 1 in 60 or 1.6%. If a woman has one first-degree relative (mother or sister) with ovarian cancer, that risk increases to 1 in 20 or 5%. If there are two first-degree relatives with ovarian cancer, that risk increases to 1 in 14 or 7%. Add in early age and that risk is even higher. Women who are members of a family with a hereditary ovarian cancer syndrome have a lifetime risk of developing ovarian cancer as high as 40%. Women with a known BRCA1 or BRCA2 germ line mutation have a 35% to 65% risk of developing ovarian cancer in their lifetime and an even higher risk of developing breast cancer.

Hereditary ovarian cancer accounts for 10% of epithelial ovarian carcinomas. In addition to the BRCA1 and BRCA2 gene-related breast/ovarian cancer syndromes, HNPCC (Hereditary Non-Polyposis Colorectal Cancer) is another important cancer syndrome worthy of mention. This hereditary syndrome, caused by a mutation in the mismatch repair genes, increases the risk of not only colon cancer, but also endometrial and ovarian cancer.

One strategy to reduce the risk of dying from ovarian cancer is the use of oral contraceptive pills for chemoprevention. Recent data suggests that the progestational component of the pill may increase ovarian epithelial apoptosis, resulting in a lowered risk. Another strategy is prophylactic oophorectomy, which dramatically reduces the risk of developing ovarian cancer. However, even with oophorectomy, primary peritoneal carcinoma can occur in 3% of cases.

Unfortunately, there is no screening strategy available currently that is sensitive and specific enough to offer to the general population. In high-risk populations, CA-125 and transvaginal ultrasonography may detect cancers earlier, but this is unproven.

CA-125 is a serum tumor marker that is elevated in 70% of women with advanced epithelial ovarian carcinoma. CA-125 is an antibody to the OC-125 antigen found on many mesothelial surfaces. Although elevated in advanced disease, CA-125 has not been shown to be an effective screening tool because it is elevated in only 25% to 50% of Stage I cancers. Furthermore, because CA-125 is elevated in so many other nonmalignant conditions like endometriosis, pelvic inflammatory disease, pregnancy, liver and renal disease, it is not reliable even if it is elevated. For this reason, CA-125 should not be used as a screening test in the general population.

Ultrasound also has been advocated as a screening test for ovarian cancer. Unfortunately, both transabdominal and transvaginal ultrasound have a high false-positive rates. In one study, 5,000 women were screened with ultrasound. Sixty-five laparotomies were neces-

sary in order to detect one case of early ovarian cancer. In a subsequent study of 1,200 women who had a strong family history of ovarian cancer and who underwent transvaginal ultrasound screening, there were 12 exploratory surgeries for every case of ovarian cancer. Current research aims at developing a more precise ability to distinguish benign tumors from those that are malignant by combining a variety of screening modalities.

Newer screening methods are currently being investigated. Serum lysophosphatidic acid (LPA) and a novel protein marker panel are two blood marker detection methods that are currently in early trials but appear very promising. Because early ovarian cancer is highly curable, it is worthwhile to continue searching for a better screening method. We are currently formulating an ovarian cancer screening trial here in Hawaii.

Contrary to what is commonly accepted, women with ovarian carcinoma do have symptoms. In a recent study of over 1,700 women with all stages of epithelial ovarian cancer, over 90% reported that they had symptoms for a duration of 1-12 months prior to their diagnosis. The problem with ovarian cancer symptoms is that they are vague and generally not gynecologic. The most common symptoms reported are abdominal bloating with increased abdominal girth, fatigue, and gastrointestinal disturbances, especially constipation, diarrhea, early satiety, urinary symptoms, abdominal and pelvic pain, and menstrual irregularities.

Patients who present with abdominal, GI, GU, or gynecologic complaints deserve a pelvic exam as part of a complete physical evaluation. Making the diagnosis of ovarian cancer can be challenging because the vague signs and symptoms, but an early diagnosis can improve a chance at a cure. Ultrasounds and CT scans are the best studies to identify a mass or ascites; however, they are currently unable to definitively distinguish benign from malignant neoplasms. A CA-125, when elevated, would indicate a higher likelihood that an ovarian tumor is malignant, especially in a post-menopausal woman. It is not appropriate to aspirate a mass or open a mass in the abdominal cavity because of the danger of seeding the abdomen with clonogenic cancer cells. In general, any patient with a suspicious ovarian mass or unexplained ascites with or without an elevated CA-125 should be referred to a gynecologic oncologist for specialty care.

Appropriate surgical staging in ovarian cancer is essential to determine the appropriate choice of adjuvant therapy. One-third of patients with presumed Stage I disease will be found to actually have Stage III disease when the appropriate staging operation is performed. In advanced disease, maximal surgical cytoreduction translates into improved survival. Our recently published data demonstrates that improved survival was seen in ovarian cancer patients who had a gynecologic oncologist involved in their care. This improved survival is most likely due to the gynecologic oncologist's familiarity with the disease and his or her extensive surgical training directed at being able to remove as much cancer as possible. Unfortunately, the majority of women who present with ovarian cancer will have extensive pelvic and intra-abdominal disease. For these women, removal of all gross disease is considered optimal and is associated with a significant survival advantage. Median survival and cure rates following optimal cytoreduction are almost double that of women in whom the surgeons could not remove all gross disease and achieve an optimal result. Cytoreduction for advanced

disease often requires removal of large pelvic tumors with en bloc resection of the uterus, ovaries, and recto sigmoid; resection of large omental tumor cakes; small bowel resection; and removal of extensive diaphragmatic and peritoneal implants. Significant surgical expertise and special training are required to perform radical ovarian cancer cytoreductive procedures.

Most patients with ovarian cancer require adjuvant chemotherapy after initial surgery. Results from cooperative group trials (i.e., Gynecologic Oncology Group, Southwest Oncology Group) have found that the best initial chemotherapy for ovarian cancer is Carboplatin plus Taxol. We have now opened the GOG here in Hawaii, allowing our patients the opportunity to be enrolled in trials offering new medications and novel combinations of existing chemotherapies with the hopes of improving survival.

GOG 182 offers triplet therapy and sequential double therapy with Platinum, Taxol, Gemcitabine, Topotecan and Doxil as upfront therapy. Another trial we have brought to Hawaii adds gamma-interferon to upfront therapy. Although most patients with advanced initial disease will achieve a complete clinical response after surgery and chemotherapy, patients with advanced (Stage III and IV) ovarian cancer have a very high recurrence rate approaching 80%. Treatment options for recurrent disease include a secondary cytoreductive surgery, retreatment with platinum and Taxol where retreatment responses can be as high as 50%, or multiple second-line therapies including Topotecan, Doxil, Etoposide, Gemcitabine, Hexalen, Ifosomide, Vinorelbine, Tamoxifen, or Herceptin. Participation in clinical trials evaluating second-line agents is now available here in Hawaii.

Cervical Cancer

Approximately 13,000 women in the United States develop cervical cancer each year, resulting in 5,000 deaths. Cervix cancer is the most common and deadly cancer for women world wide. Fortunately though, as a result of wide-spread cancer screening with the pap smear, cervix cancer deaths in the United States are a fraction of what they were just 50 years ago.

The risk factors for cervical cancer are well known. Most of them are associated with risk factors for contracting a sexually transmitted disease. Women who begin intercourse at an early age are at a higher risk. Those who have had multiple sexual partners or have a partner who themselves have had several partners place themselves at higher risk. Smoking is also a strong a risk factor as is lower socioeconomic status and a history other of sexually transmitted diseases.

Cervical cancer is a sexually transmitted disease and the human papilloma virus (HPV) is the causative agent. While up to 50% of the United States population is infected with HPV, only a small minority ever develop cervical lesions. This is because only a handful of high-risk types lead to cancer. The great majority of women infected with HPV will never develop cancer.

The pap smear is a screening test for cervical cancer that detects abnormalities in the cervical cells caused by HPV infection. A woman should have her first Pap test and pelvic exam at the age of 18 or after the first onset of intercourse, whichever comes first. If a woman is in a low-risk category after three consecutive, normal annual examinations, the Pap test may be performed somewhat less frequently. However, if either the woman or her male partner is in

a high-risk category, the Pap test should be continued to be performed on an annual basis for a lifetime. In today's society, most women are considered to be at risk.

The Pap smear is not a completely accurate test. For any single Pap smear, the false-negative rate is 20%. Fortunately, the latency period for a precancerous lesion to develop into invasive cancer of the cervix, while variable, is usually measured in years. Regular screening of the cervix should identify a pre-malignant cervical lesion, which may be effectively and simply treated by a specialist in the area. Of note, half of the women with cervical cancer have never had a Pap smear, and one quarter of the cases (41%) of the deaths occur in women 65 years of age or older. It is important to note that women who are postmenopausal still require Pap smear screening yearly. Newer methods of screening are currently being investigated. One approach is the detection of a high-risk vaginal HPV infection as a prediction of likelihood to develop cervical cancer. Currently, HPV screening is only useful in the context of a mildly abnormal (ASC-US) Pap smear.

Despite the limitations of a Pap smear, three yearly Pap smears will lower the risk of dying from cervical cancer by over 90%. Abnormal Pap smears result in colposcopic evaluation and directed cervical biopsy. In some cases, pre-malignant disease can be followed over time. Other more extensive pre-malignant disease is treated with cryotherapy, laser vaporization, cervical conization, hysterectomy or more commonly, LEEP.

For women diagnosed with invasive cancer, the signs and symptoms may be silent until there is advanced disease. Some women may report postcoital bleeding, a foul vaginal discharge, or other abnormal bleeding. Signs of advanced cancer may be pelvic pain, unilateral leg edema or pain. A pelvic mass or grossly visible cervical lesion may also be noted.

Patients diagnosed with invasive cervical cancer should be referred to a gynecologic oncologist. Very early disease in selected patients who desire preservation of fertility can be treated conservatively with a cervical conization or radical trachelectomy. Surgical care of advanced local disease is accomplished with radical hysterectomy and pelvic lymphadenectomy.

For those cancers that are too large for radical hysterectomy or ones that have spread beyond the cervix, chemoradiation therapy is the treatment of choice. Recent studies have shown that a combination of radiation plus cisplatin offers the best hope for women with advanced cervical cancer. External beam radiation targets both the primary tumor and the other pelvic tissues, including the pelvic lymph nodes. This is followed by two or more radiation cervical implants, also known as brachytherapy. It has been recently demonstrated that the use of concurrent cisplatin-based chemotherapy with radiation significantly improves the chances of survival by acting as a radiation sensitizer and also decreasing the chance of distant spread.

Pre-malignant cervical disease, dysplasia, has a nearly 100% five-year survival. Early invasive disease is highly curable with radical surgery or radiotherapy and five-year survival rates are nearly 90%. Unfortunately, distant disease is virtually incurable. Clinical trials utilizing newly developed drugs are currently available in Hawaii. In addition, there are now HPV therapeutic vaccinations designed to stimulate the immune system against metastatic disease in early trials.

The management of recurrent cervical cancer is problematic. For those women who have not received primary radiation as initial therapy, chemoradiation may be curative or palliative. An occasional isolated soft-tissue recurrence may be treated by resection with long-term survival. The use of chemotherapy is palliative in nature and has relatively little impact on the length and quality of life.

Vulvar and vaginal cancer, although uncommon, are easily treatable if caught early. Both are similarly thought to be caused by the HPV virus.

Promising research is now under way in the field of cervical cancer prevention. The most exciting work involves the development of a vaccine against the human papilloma virus. Vaccines are being designed for both prophylaxis and therapy. At the University of Hawaii, we have opened a new HPV vaccine trial for the prophylaxis of HPV infections. To be enrolled, women must not have been infected with the HPV virus. If this trial is successful at preventing HPV infection, it will have the most significant impact in history on cancer prevention. Of critical importance is to encourage participation of women with cervical cancer and other malignancies in clinical trials. Adult participation in clinical trials is currently less than 5% across the nation. If we are to make any progress against this disease, development of new treatments, and hence, clinical trial participation is absolutely essential.

Endometrial Cancer

Endometrial cancer is the most common pelvic malignancy in the United States affecting nearly 40,000 women a year. Six thousand five-hundred women died of endometrial cancer in the year 2000, representing a dramatic 224% increase in the past decade.

It is hypothesized that there are two natural history courses for endometrial cancer: Type 1, which is estrogen related, and Type 2, which is unrelated to estrogen stimulation and much more common in the United States. Type 1 is seen in younger, heavier patients, tends to be lower grade, and involves exogenous estrogen. Type 2 occurs in older and thinner women as well as those endometrial cancers that have a genetic basis, especially hereditary non-polypoid colon cancer (HNPCC).

Several constitutional factors have been identified in women who develop endometrial cancer including obesity, nulliparity, late menopause, unopposed estrogen, diabetes, and hypertension. Obesity is the greatest risk factor. Atypical endometrial hyperplasia is the pre-malignant precursor of Type 1 endometrial cancer. Virtually all of these patients, if left untreated, will develop invasive endometrial cancer over time. Fortunately, a simple hysterectomy will eliminate the chance of metastatic disease. Women with a history of breast cancer who take Tamoxifen have a slightly increased risk of endometrial cancer and uterine sarcoma. Abnormal bleeding while on this medication always prompts immediate investigation with endometrial sampling. Interestingly, Raloxifene does not increase the risk of endometrial cancer.

Over 90% of all women with endometrial cancer present with postmenopausal bleeding. There are no satisfactory ways to screen for endometrial cancer. Pap smears do not screen for endometrial cancer. However, Pap smears revealing atypical glandular cells or malignant endometrial cells frequently lead to the diagnosis of endometrial cancer. Women with postmenopausal or abnormal

perimenopausal bleeding should be evaluated with endometrial biopsy. High-risk women over 35 with menometrorrhagia should also be biopsied. Ultrasound can be useful in the evaluation of abnormal bleeding. If the endometrial stripe is less than 5mm, the risk of endometrial cancer is virtually elevated. Recurrent bleeding is an indication for endometrial sampling even if an ultrasound is normal. The survival of patients with endometrial cancer is correlated with the stage of disease. Endometrial cancer is highly curable if caught early. Stage I disease is cured in over 90% of cases while distant disease realizes only a 10% long-term cure rate.

Surgery is the cornerstone of endometrial cancer therapy. Once a diagnosis of endometrial cancer is made, the patient should be referred to a gynecologic oncologist. With the exception of very small, early, non-invasive, grade I lesions, all patients should undergo a staging procedure including hysterectomy, salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. If more extensive disease is found, radical resection is indicated.

Recent studies have confirmed the benefit of complete lymphadenectomy in endometrial cancer patients. In the year 2000, a University of Alabama study found an improvement in survival in even early staged patients undergoing complete lymphadenectomy. This is presumably due to the resection of clinically occult microscopic metastatic foci.

Recent publications have called into question the role of radiation therapy for patients with locally advanced endometrial cancer. A large Gynecologic Oncology Group trial (GOG 99) found no statistical improvement in survival for patients with high-risk early and locally advanced disease treated with adjuvant radiation therapy, although pelvic disease was controlled.

Advanced and recurrent endometrial cancer can be treated using several therapies, sometimes quite successfully. A current GOG trial open in Hawaii offers radiation therapy, chemotherapy with platinum, Taxol, and Adriamycin, as well as hormonal therapy with Tamoxifen and Megace.

Lower grade endometrial cancers are estrogen receptor positive and frequently have dramatic responses even with widely metastatic disease to hormonal therapy. Because of the estrogen receptors seen in endometrial cancer, hormone replacement therapy has traditionally been withheld. Retrospective studies, however, have found no detriment to survival with HRT. The GOG has an ongoing prospective randomized-blinded trial to answer definitively this very question. Patients in Hawaii diagnosed with endometrial cancer can choose to be a part of this study.

The future includes tumor biology. Gynecologic researchers have turned to molecular biology in an attempt to elucidate the etiology of these cancers. Recent research describing DNA ploidy, oncogene, and tumor suppressor gene mutations common to these malignancies is providing a basis for molecular genesis of these cancers. For example, DNA ploidy is an independent quantifiable predictor of progression-free survival in patients with endometrial cancer. Aneuploidy implies the presence of an abnormal quantity of genomic material and imparts a less favorable prognosis. The over expression of several regulatory genes, such as c-fms, K-ras, HER-2/neu, and p53, also may harbor prognostic significance in endometrial cancer. Molecular events may determine various behavioral characteristics of tumors. Therefore, the identification of molecular variables may

assist clinicians in determining patient risk status and in selecting treatment options.

Beyond molecular research, reducing obesity in the United States would be an immediate way to reverse the increasing incidence of endometrial cancer. Additionally, the use of oral contraceptives in high-risk patients under 50 would dramatically lower the risk of endometrial cancer. Finally, persuading patients to seek medical attention for abnormal bleeding and encouraging physicians to perform evaluations with any signs of bleeding would go a long way toward maximizing survival.

Conclusion

As a physician and scientist, there is no better time in history to be involved in the understanding and advancement to treatment for gynecologic cancers. So much is being discovered every day. There are exciting new serum markers for the detection of early ovarian cancer, prophylactic vaccinations that could eliminate cervical cancer all together, and advances in the surgical treatment of endometrial cancer. Part of our mission is to allow our patients the opportunity to participate in potentially life-saving treatment and screening trials, many of which are available right here at home in Hawaii.



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Compiled by Carolyn S.H. Ching and Marlene M.A. Cuenco

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The Eyes Have It!

The world's busiest airport, Heathrow in London, has begun to study a new security program of passenger recognition by using the iris. *Eyeticket*, the technology device, can measure up to 240 unique points on an individual iris (fingerprints have 20 to 40), then convert the points to code, and compares that with information stored on a data base to find a precise match. To get into the program passengers can enrol at airport-based clubs. The system uses no laser or harmful light, and is hygienic since no part of the body is touched. The system will speed up check in, visa processing, and hotel registration. Virgin Atlantic and British Airways are already operating iris recognition stations in lounges at New York's JFK, and Washington D.C.'s Dulles Airport. Once the program gets into wide use, the frequent flyer and the business flyer will be able to avoid the lengthy security delays. As the Israeli security consultant said, "America doesn't have an airline security system, it has a program to annoy people." *Eyeticket* should help.

Arresting Development: Joint Venture In Britain!

Following in the footsteps of most European countries (Holland, Germany, Switzerland, Belgium) Great Britain has decriminalized marijuana for the casual user. The change is based upon a successful experiment begun last year in Brixton, a South London neighborhood. The police chief declared that arrests for smoking cannabis were a waste of time and money. Technically, the drug remains illegal, but attention will be directed at those selling, and possession of small amounts of cannabis will be ignored. Prime Minister Tony Blair supported the change, and said it will give police more time and resources to attack violent crime and the use of hard drugs such as heroin. The premise is that it does no good to incarcerate these people where they get no treatment, but do get easy access to all sorts of drugs. The trend in Italy, Portugal, Spain and Luxembourg is to decriminalize all drugs, including cocaine and heroin, and to treat drug use as a health problem. Drugs are still considered dangerous, but the intent is to educate young people and direct them away from the nightmare of addiction.

The Road To Surgery Is Paved With Good Inventions.

Sixty years ago at a small town in Nazi-occupied Holland, Dr. Willem Kolff was aware that with kidney failure, the body has no way to remove waste. He constructed a device made of sausage casings and a Ford water pump, and ultimately fashioned an artificial kidney. After moving to the United States he devised an intra-aortic balloon to help pump blood in patients with cardiac failure. It was the basis for a pump used in hundreds of thousands of patients every year. He designed the first artificial heart implanted in Barney Clark in 1962. Now age 91, his latest device is a prototype artificial lung taped together with some plastic tubes that he hopes to test on sheep next year. He doesn't bother with patents since he says you don't get rich from artificial organs. He is being awarded the Lasker Award for medical innovation given by the Albert and Mary Lasker Foundation for prolonging the life of millions. It's about time.

Why Is A Question We Stopped Asking A Long Time Ago.

Responding to the "snack police," Frito-Lay is trying again with broccoli laced potato chips, and using healthier fats in cooking. Hey, we already struggle to endure anti groups stretching from anti-tobacco and anti-God, to anti-peanuts on the airplane. But, give me a break, "snack police?" Face it, people don't really want "healthy" snacks. Frito-Lay previously failed with their fat-free chip made with olestra which is remembered best for causing belly aches, and McDonald's McLean low-fat burger was a flop. It is not the fault of Frito-Lay, Pizza Hut, Coke and Pepsi, and the fast food industry that people overeat, that kids pork out in front of the TV, and that serum fat fractions go off the board. What ever happened to regular exercise, intelligent eating, common sense, and wise choices? Eventually on the agenda for these insufferable anti-whatever people will be the Orwellian anti-thought police, and I am likely to be an early victim.

Television Adage "If It Bleeds, It Leads."

A recent article offered in the Journal of the American Medical Association delved into the practice of commercial film presentations in hospitals wards, emergency rooms and even operating rooms. Commercial interests claim

potential benefits are providing education for the public and demystifying many conditions. On the negative side are the issues of privacy and editing, and appropriate use of the film. The issue of privacy is most important, and appropriate informed consent must be obtained before any filming. However, hospitalized patients may not be able to understand informed consent, and in the event of an untoward event, what about medico-legal problems? The AMA Council on Ethical and Judicial Affairs has outlined parameters for filming patients in health care settings, but hey, why encourage any such filming? The education and history television channels together with PBS programs like NOVA already provide volumes of medical information and detailed photography. These nosy, titillating TV people should seek their macabre stories at the wrestling arena.

Is This News? Ignorance And Politics Triumph Over Science.

Sometimes the environmental protectors of this world, don't even realize when they are desperately wrong. On the Senate agenda is endorsement of the Stockholm Treaty which would virtually eliminate the use of DDT in the world. Here are some facts, and you can look them up:

1. DDT is absolutely harmless to human beings.
2. Between 1946 when DDT was introduced in Sri Lanka and 1964, the number of cases of malaria dropped from 3 million to 29, with zero deaths.
3. In India in the 1940s, 75 million people contracted malaria with 800,000 deaths each year, and by 1961 the number of those infected had dropped to 50,000 thanks to DDT.
4. Repeated studies have tried to prove that DDT causes fragile bird egg shells, but at best those efforts are inconclusive. Nonetheless, this tale is accepted almost universally, thanks to Rachel Carson and other non-scientists (In 1971 I had the opportunity to inspect and evaluate pelican nests and egg shells on the Channel Islands with a team from San Jose State University). Many pollutants, such as lead and petroleum products alter calcium contents, and do cause fragile egg shells.
5. After the EPA hearings in 1972, the chief examiner stated, "DDT is not carcinogenic to humans. The uses of DDT under the registrations involved here do not have a deleterious effect on fresh-water fish, estuarine organisms, wild birds or other wildlife."
6. In 1972, EPA administrator lawyer William Ruckelhaus, attended none of the hearings, admitted he did not read the report, and arbitrarily banned the use of DDT, possibly at the direction of the President, Richard Nixon.
7. According to the World Health Organization, "Sub-Saharan Africa is the worst affected area for malaria with about 90% of all malaria cases and 80% of deaths. This means about 1.5 to 2.7 million people, mainly children, die each year from malaria." The Stockholm Treaty on Persistent Organic Pollutants would permit some use of DDT, but the practical effect will be to discourage its use. Some nations that previously used it have already stopped. But, in Stockholm malaria isn't much of a problem, and who cares about a few million Africans and Asians.

ADDENDA

- ❖ Starfish have eight eyes; one at the end of each leg.
 - ❖ The first known contraceptive was crocodile dung used by Egyptians in 2,000 B.C.
 - ❖ In Sheridan, Wyoming, a man has been struck by lightning three times in eight years. He claimed, "This is harassment, pure and simple," and filed a lawsuit against God!
 - ❖ Why is there a planet named Pluto, but none named Goofy?
 - ❖ In Mendota Heights, Minnesota, a high school cheer leader filed a \$50,000 lawsuit against her school for being demoted after she was caught smoking and drinking alcohol.
- 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.

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