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Contents

Norman Goldstein MD ................................................................. 212

From the Associate Editor: Introducing... “Na Kauka O Hawaii”
William W. Goodhue Jr. MD ..................................................... 213

Na Kauka O Hawaii: Dwight Baldwin MD (1798-1886)
Hawaii Medical Association Auxiliary .................................. 214

Commentary: Kimo’s Rules
Shay Bintiff MD ................................................................. 215

Intestinal Parasites of the Pacific
Ethan A. Small BA, Alan D. Tice MD, and Xiaotian Zheng MD, PhD .......... 216

Lamivudine Prophylaxis for Chemotherapy Induced Reactivation Hepatitis B: A Case Report and Review
Shane J. Mills MD, Jeffrey L. Berenberg MD, and Fernando Ramos MD .......... 220

Medical School Hotline: Student Profile: Class of 2007, John A. Burns School of Medicine (JABSOM)
Satoru Izutsu PhD ........................................................................ 223

Cancer Research Center Hotline: Targeting Oncogene Expression in a Childhood Cancer
Matthew C. Tuthill PhD and Randall K. Wada MD .................. 224

Classified Notices ................................................................. 225

Weatherwane
Russell T. Stodd MD ........................................................ 226

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

Lele Kawa

Cliff jumping was one of the favorite sports of old Hawaii.
Editorial

Report to the Hawaii Medical Association Annual Meeting

The Journal is very alive and doing well, thanks to the local and national advertisers and Michael Roth, our advertising executive; Drake Chinen, our editorial assistant; Dietrich Vare, our Big Island cover artist; the many authors and peer review panel members; Russell Stodd continuing his excellent Weatherwane; contributors from the Cancer Research Center, School of Medicine; and Hawaii Medical Library Staff yearly index preparation.

After a sabbatical, Henry Yokoyama has resumed his popular News and Notes with the July 2003 issue.

The big news at the Journal is the appointment of William W. Goodhue, Jr. MD, as Associate Editor. With Bill’s experience as a teacher and writer, and his boundless energy, the Journal is expanding its neighbor island coverage, native Hawaiian medical subjects and special issues.

On a personal note, I am not retiring. My wife, Ramsay, and I have moved to Maui, where I used to see patients monthly (as well as on Kauai and the Big Island). We maintain our Historic Tan Sing Building in Chinatown, where Ramsay has the Ramsay Museum and I have my Dermatology practice, where I see patients three days per week. I then travel to Maui for four days, living upcountry in Kula, where I can write, read, and with the benefits of phones, faxes and e-mails, continue my many medical and non-medical activities. I will also host an internet radio program on Voice America, the Skin You Live In from my studio on the slopes of Haleakala.

The Journal and the Foundation

The Hawaii Medical Journal is the sole publication of, by and for Hawaii physicians, researchers, residents and students. Nowhere else can one find the activities of the John A. Burns School of Medicine, the Cancer Research Center of Hawaii, and the Hawaii Medical Library in one publication.

For more than 60 years the Journal has been sent to every member of the Hawaii Medical Association. The bylaws of the HMA mandates that members receive the Journal as a benefit of membership. At the annual meeting of the HMA in 2002, subscription to the Journal was made voluntary. This year funding for the Journal was left out of the HMA proposed budget for ‘04.

At the House of Delegates Pat Blanchette MD, president of the Board of Directors of the Hawaii Medical Foundation, formally called the Reference Bureau, proposed that the Journal be administered by the Foundation and that funding be included in the HMA ‘04 budget for one more year, while details of funding through the foundation are worked out. The future dues structure will include subscription to the Journal, in order to remain in compliance with the bylaws.

As we go to press, the Journal is in preliminary discussions with the Hawaii Medical Foundation and we welcome your comments.

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Clarice B. Taylor’s “Tales about Hawaii” column in the territorial Honolulu Star-Bulletin commemorated people, events and institutions shaping the history of Hawai‘i nei. Although the column generally appeared on the last page of the newspaper, it was often the item many readers turned to first. Our new column, to be included in every other issue of the Hawaii Medical Journal (HMJ), will focus on commemorating physicians of Hawai‘i (Na Kau‘a o Hawai‘i) from the early 1800s to the present, by providing biographical sketches and, when available, photographs.

Principal source materials are twofold: the In Memoriam—Doctors of Hawaii seven volume collection at The Mamiya Medical Heritage Center at Hawaii Medical Library (HML) describing doctors practicing in Hawai‘i and now deceased, and the Hawaii Medical Association’s (HMA) Senior Physicians Committee listing of living, retired physicians.

In Memoriam—Doctors of Hawaii’s compilations come from source materials including HMA archival listings, newspaper clippings, Who’s Who and Men of Hawaii listings and when possible contact with the doctor’s family, close personal friends and professional associates. This seven volume series began in the early 1950s as a project of the HMA Auxiliary, with the first two volumes being completed in time for presentation to the HMA in 1956, on the occasion of its 100th anniversary. Mrs. Betty Katsuki, widow of Robert Y. Katsuki, M.D., worked with other HMA Auxiliary volunteers for more than 30 years to complete the collection of biographical sketches of 621 doctors and 407 photographs listed in the 1986 Index to: In Memoriam: Doctors of Hawaii. The project was resumed in the mid-90s by HML volunteers Ann Catts, M.D., and Florence Chinn, M.D., with 63 additional biographical sketches, and is again ongoing. Work is currently overseen by John A. Breinich, MS, Executive Director, HML, and Laura E. Gerwitz, MA, MLIS, Reference Librarian/Archives. Online access to this database is available through links at http://hml.org/mmhc/.

Members of the HMA Senior Physicians Committee will also be approached from time to time for interviews as a basis for biographical sketches in Na Kau‘a o Hawai‘i. Many of these doctors already have video and oral histories in the HML Medicine in Hawaii: Oral History Series.

Biosketches will be presented with certain themes; for example, doctors who took care of Hawai‘i’s kings, queens and ali‘i; missionary doctors; doctors who played significant roles in combating epidemics (plague, cholera, typhus, typhoid fever) in the 1800s and other infectious diseases (tuberculosis, leprosy); plantation doctors; doctors of Kaua‘i, of Oahu, of Maui, of Molokai, of Lanai, of the Big Island. There will be overlaps among these themes. Our inaugural biosketch in this issue is of Dwight Baldwin, M.D., because with a birthdate of 1798 he is one of the earliest of physicians practicing in Hawai‘i on whom data is available.

Enjoy!

From the Associate Editor

William W. Goodhue Jr. MD
Associate Editor, Hawaii Medical Journal
Dwight Baldwin was born at Durham, Connecticut, on September 29, 1798, the son of Seth and Rhoda (Hull) Baldwin. His first two years of college work were done at Williams College, Williamstown, Massachusetts, and from there he went to Yale from which he graduated in 1821. From 1821 to 1824 he taught school in Kingston and Catskill, New York, and in 1824 he began the study of medicine while teaching at Durham, New York. Dropping the study of medicine in 1826, he entered the Auburn Theological Seminary, graduating in 1829.

As a minister young Baldwin volunteered to join the Fourth Missionary Company being made up to go to Hawaii, but the demand for doctors outweighed the need for ministers, so he returned to Harvard in 1828-1829 and attended a course of medical lectures. However, he did not have time to wait for his official medical diploma and, at the advice of the Prudential Committee of the Mission Board, accepted a diploma as Master of Science. In the years to come, Dr. Baldwin’s lack of a medical diploma was to cause him great embarrassment. Although he was obviously as well qualified as any of his professional peers and practiced for some 27 years, the Hawaii Medical Society refused to grant him a license until he could produce documentary proof of a medical degree. In 1859 he belatedly received word from Dartmouth College in New Hampshire that they had granted him an honorary medical degree.

Dr. Baldwin married Charlotte Fowler at Northford, Connecticut, on December 3, 1830. On December 28 the young couple sailed from New Bedford, Massachusetts, as members of the Fourth Missionary Company. After a voyage of 161 days aboard the "New England", they arrived in Honolulu on June 7, 1831.

For the first six months the Baldwins were stationed at Honolulu, and on November 26, 1831, their first child, David Dwight, was born. Seven other children were born to the doctor and his wife: Abigail Charlotte (Mrs. William D. Alexander), Mary Clark, Charles Fowler, Douglas Hoapili, Henry Perrine, Emily Sophronia (Mrs. William O. Atwater), and Harriet Melinda (Mrs. Samuel M. Damon). Mary and Douglas died in early childhood.

In January, 1832, the Baldwins were assigned to Waima, Hawaii, where they remained until February, 1835, when the family moved to Lahaina, Maui, hopeful that the drier climate there would prove beneficial to the throat ailment troubling Dr. Baldwin. When the change brought little improvement, the doctor took a trip to the Society Islands. He was gone for six months, returning in September, 1836, completely cured.

During his years at Lahaina Dr. Baldwin preached every Sunday in Hawaiian at the Waine Church and often preaching assignments took him to other parts of Maui. He supervised all the church schools (numbering 22 in 1849) and was instrumental in building a seaman's chapel. During the smallpox epidemic of 1853 Dr. Baldwin worked so effectively that out of a total of 10,000 deaths in the Islands, there were only 250 fatal cases on Maui. In an attempt to cure the cases of leprosy which he treated on Maui, he became intensely interested in the disease and experimented with many types of drugs. He was also an advocate of all movements to diminish the sale and use of liquor and tobacco, and was the author of an essay on the subject which won a prize offered in the United States. Somehow the doctor found time for agricultural and horticultural experiments and was a charter member of the Royal Hawaiian Agricultural Society when it was organized in 1850.

In 1856 Dr. and Mrs. Baldwin revisited New England, going by way of Cape Horn and returning on January 8, 1858, via the Panama Canal. The doctor also made a trip to the Marquesas in 1862 as a mission delegate.

Forced to resign in September, 1868, due to paralysis, Dr. Baldwin moved to Honolulu in 1870 and he and Mrs. Baldwin made their home with their daughter, Abigail. In spite of his disability, the doctor taught at the native Theological School in Honolulu from 1872 to 1877.

On January 3, 1886, Dr. Baldwin died in Honolulu at the age of 87. Mrs. Baldwin predeceased him on October 2, 1873.

Dwight Baldwin MD
1798 – 1886
by Hawaii Medical Association Auxiliary

Mumiyo Medical Heritage Center, Hawaii Medical Library.
Several years ago, a very popular tee shirt was printed in Hawaii. There were no sandy beaches, beautiful women in bikinis or exciting surf scenes. No, it was quite simply a “therapy shirt”... and it sold like hot cakes!! Kimo’s Rules continues to be a very popular item, not only for the humor in some of the rules, but mainly for the wisdom so simply expressed. See if you don’t agree with me. Here are Kimo’s Rules:

1. Never Judge a Day by the Weather
2. The Best Things in Life aren’t Things
3. Tell the Truth... There is Less to Remember
4. Speak Softly and Wear a Loud Shirt
5. Loosen Up... The Unaimed Arrow Never Misses
6. He Who Dies with the Most Toys, Still Dies
7. Age is Relative... When You’re Over the Hill... You Pick up Speed
8. There are Two Ways to Get Rich... You Can Make More or You Can Require Less
9. What You Look Like Doesn’t Matter... Beauty is Internal
10. No Rain... No Rainbows

Ah, such wisdom... and so little time. My family will likely never forgive me, but I started reading Kimo’s Rules to my granddaughter, Ileiana, when she was five years old. When she didn’t completely understand a rule, she would ask the most profound questions. Like Rule #4... she asked, “why do I have to speak softly if I have a red shirt on, Granny... maybe I want to shout... but maybe that will scare people, yes??” And question #2, my all time favorite: “Is a hug a thing, Granny? Or like camping out with daddy on the beach, is that a thing? Cause you know, those are the best!!” Now at age 8, she constantly reminds us all to “tell the truth,” and to “always look for rainbows!” We even made up a game called “Name that rule”... One of us writes down a number, and the other has to guess what rule your are thinking of. If you are wrong, you have to tell a story about that rule. WOW... have I heard some “out of the mouth of babes” stories!!!

Bringing closure to this moment of joyful sharing for me, I can sum it all up with these words: Kimo has real clarity on what is important in our lives. The “Rules” reflect what we all know about the “Aloha Spirit”... that to be generous and loving, especially with ourselves, will go a long way. Kimo’s Rules are like a large dose of positive energy and thinking, the kind of focus that builds strength and resilience.

Editorial Comment:
Sharon Shay Bintliff MD, FACEP, FAAP, is Emeritus Professor of Surgery and Pediatrics at the John A. Burns School of Medicine. She still practices Emergency Medicine as the Medical Director of the Emergency Department at the Kauai Veterans Memorial Hospital on Kauai.

Dr. Bintliff presented “Kimo’s Rules” at the recent Hot Spots in Dermatology 2003 on Maui. With her permission, we are presenting the Rules to readers of the Journal. She has lived in Kamuela on the Big Island for the past 10 years and continues “to have a full life canoe paddling, golfing, hiking, and working on her Sandalwood Tree Farm.”
Intestinal Parasites of the Pacific

Ethan A. Small BA, Alan D. Tice MD, Xiaotian Zheng MD, PhD

Abstract
Information about intestinal parasites in Hawaii and the Pacific is not current. We reviewed reports on fecal samples obtained from two laboratories and found recovery rates of 9.3% in Hawaii, 14.2% in Saipan, 18% in Rota and 9.5% in Guam. The most frequently identified parasites were Blastocystis hominis (7.6%), Giardia lamblia (1.2%), and Entamoeba coli (0.7%). Although the incidence and types of organisms have changed with time, physicians in Hawaii should continue looking for intestinal parasites.

Introduction
Intestinal parasites have been a scourge of mankind for millennia. They have adapted to numerous habitats and hosts while spreading throughout the world. Improvements in sanitation and medications, however, have interrupted their life cycles in many instances. Consequently, they have lost their foothold in numerous countries. While the impact of modern medicine has been dramatic in Hawaii, intestinal parasites remain a common cause of disease. Continued immigration of Pacific Island and Asian peoples and travelers bring strongyloides, hookworm, and ascariis while possibly serving as reservoirs for transmission. Parasites may remain asymptomatic for years or may present with symptoms outside the gastrointestinal tract. Some of the most frequently recognized parasites in recent years include Cryptosporidium parvum and Blastocystis hominis; they remain threats because of their presence in natural reservoirs and public water supplies. The chances of eradicating these organisms are small. Both are thought to be transmitted via a fecal-oral route. C. parvum has survived in public water supplies due to its small size (passes through <1μm filters) and resistance to chlorination. Controversy exists as to whether B. hominis is a pathogenic versus commensal organism. However, outbreaks with symptoms have been reported.

The Center of Disease Control estimated a parasite burden of 20% in the United States during 1987. With advances in sanitation and medication, surveillance and reporting activities were reduced, such that there is little record of the incidence of intestinal parasites or changes that have occurred since. In addition, “new” microorganisms are being recognized that are not visible with standard ova and parasite diagnostic tests. These require special stains and identification techniques in the laboratory.

Reports of intestinal parasites in Hawaii or other Pacific Islands are scarce. Prior publications in 1961 and 1975 indicated 12 and 13% recovery rates. The 1975 study was primarily of school aged children in Oahu with the majority of positive samples occurring in foreign-born subjects. Information about parasitic diseases in other Pacific Islands has been limited to reports of small outbreaks rather than survey results. Old reports do not indicate the distribution of cryptosporidia, microsporidia or blastocystis as they have only recently been identified and reported as pathogens.

Because of the presence of endogenous parasites in Hawaii and the potential for importation from other islands in the Pacific, we set out to gather information from two laboratories in Oahu that perform a large number of tests for ova and parasites from specimens collected in Hawaii as well as other islands.

Methods
MedLINE was searched for information about intestinal parasites. Attempts were made to contact the ministries of health in Hawaii, Australia, New Zealand, Saipan, and Guam plus the London School of Hygiene and Tropical Medicine, the Center for Disease Control, the World Health Organization, and the Swiss Tropical Institute through web pages and e-mail.

Laboratory information was gathered from Diagnostic Laboratory Services (DLS), a commercial laboratory based in Honolulu and from the microbiology department at Tripler Army Medical Center (TAMC). DLS processes samples from all the islands of Hawaii and from Guam, Saipan, and Rota. It was not possible to determine whether samples submitted by Hawaii physicians were taken from patients residing outside of Hawaii. TAMC receives samples from military bases all over the Pacific; however, samples were not identified by geographic source. Both laboratories are certified by the College of American Pathologists for ova and parasite examinations. DLS screens for giardia in all samples, but does not routinely look for cryptosporidium or cyclospora without a special request. TAMC routinely screens for giardia in all samples, and uses Direct Fluorescence Antibody (DFA) stains to screen for giardia and cryptosporidium in all children under five years old. Identification of blastocystis, hookworm, taenia, and Entamoeba sp.

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HAWAI`I MEDICAL JOURNAL VOL 62 OCTOBER 2003 216
was part of a routine parasitology work up at both laboratories. This included examination of stools with standard concentration and permanent staining methods. Laboratory records for stool samples collected for ova and parasite examinations were accessible from October 1, 2001 until March 1, 2002 through DLS, and November 2001 through February 2002 for TAMC. It was not possible to determine the reason for ordering tests nor the frequency with which fecal ova and parasite examinations were done in any specific population.

Information about specimens was collected without patient identifiers. The study was considered exempt from the Department of Health and Human Services Regulation regarding patient confidentiality and informed consent by the Committee of Human Studies at the University of Hawaii.

Results
Findings for specimens reported are displayed in table 1. Results demonstrate a percentage of parasite recovery in all specimens from Saipan (14.2%), Guam (9.5%), Rota (18.5%) and Hawaii (9.3%). The percentage of positive results was 11.0% in DLS samples compared to 7.4% in samples from TAMC. Personal communication revealed that the majority of TAMC samples are from active duty, reserve, retired military personnel or their families.

The types of parasites identified by the DLS and TAMC labs are also presented in table 1. The parasite recovered most frequently was B. harninis found in 60.9% of positive stool samples in Hawaii and 50-77% in other Pacific islands. Giardia was only recovered in 10.7% of positive Hawaii samples and 0-50% in non-Hawaii Pacific Island samples. Entamoeba histolytica was found in samples submitted from physicians in Hawaii. Cryptosporidium was not reported in any sample from DLS or TAMC. Ascaris, necator, taenia, trichuris and other helminths were infrequent findings. Strongyloides stercoralis was only identified in one sample from Guam and one from Saipan.

Discussion
The system used in this study is not able to determine the true incidence or prevalence of intestinal parasites in the different populations studied. To do so accurately would require large surveys of the peoples of the regions reported which would not be practical. Furthermore, it was not possible to determine whether samples submitted from geographic regions represented follow-up samples from individual patients, thus falsely raising or lowering any calculations of prevalence or incidence. However, the data collected does provide current information about the primary pathogens recovered from various regions in the Pacific, allows for rough comparisons of recent results with old surveys, and demonstrates trends which may appear to be taking place over the last 27 years. Conclusions based on this data are limited in that the criteria for collecting the reported specimens are not clear and undoubtedly vary from one source to another.

There has been an apparent decline in the identification of ova and parasites compared to the older studies of 1974 and 1987. This likely reflects improved sanitation, public health measures, and modern anti-parasitic medications. Giardia was reported to be the most frequently identified intestinal parasite in the United States. It was found in 7.2% of all reported stool samples in 1992 with the greatest recovery rate occurring in the Midwest. Desowitz identified giardia in 4.1% of samples taken from Hawaii school aged children in 1974. A recent overall decrease in recovery may be due to greater public awareness of giardia in outdoor waters and travel safety measures. Children ages 0-5 years old, as used in Desowitz’s study, demonstrate a higher incidence than other age groups.

The prevalence of giardia in the United States may be underrepresented since only 20-50% of patients show signs of illness and patients may not shed cysts in their stool on a daily basis. It is unlikely that giardia is underreported in this study as DLS and TAMC routinely screen for the protozoan during standard ova and parasite detection procedures.

The recovery of Strongyloides stercoralis in Guam and Saipan reinforces the need to look for parasites in immigrants from these regions. The nematode is found world wide, but primarily in tropical climates. Patients may remain asymptomatic carriers for many years. Serious disease may occur in asymptomatic patients who later become immunocompromised. Strongyloides may also cause a variety of extra-intestinal symptoms including cough, pruritis, and weight loss. Hyperinfective strongyloidiasis is often fatal in immunocompromised individuals; frequently leading to acute respiratory distress syndrome and E. coli septicemia.

It may be beneficial to screen for Strongyloides in patients who are HIV positive or about to begin immunosuppressive therapy, particularly if they originate from or traveled to an endemic region.

The discovery of B. hominis as the most frequently recovered parasite is of interest. It was reported in only 2.6% of all stool specimens in the 1987 CDC national survey. Desowitz did not report B. hominis in 1975, likely due to differences in laboratory staining and reporting requirements. Over the last 25 years, numerous studies have been undertaken to determine whether B. hominis is responsible for gastrointestinal disease. Amin recorded B. hominis as the most frequently identified parasite (23%) recovered from 2896 patients in the United States during 2000. Doyle reported diarrhea, flatulence, and abdominal pain in a group of 143 patients with B. hominis as the only identified organism on studies for bacterial and para-
Table 1.—Percent recovery of parasites from positive stool samples submitted for ova and parasites to Tripler Army Medical Center (TAMC) and Diagnostic Laboratory Services (DLS). Samples from DLS were collected between October 1, 2001 and March 1, 2002. Samples from TAMC were collected between November 27, 2001 and February 27, 2002.

<table>
<thead>
<tr>
<th>Stool Samples from TAMC, N=277</th>
<th>Stool Samples from Diagnostic Laboratory Services</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hawaii, N=2394</td>
</tr>
<tr>
<td>Total Number Positive Stool Samples</td>
<td>20</td>
</tr>
<tr>
<td><strong>Parasite</strong></td>
<td></td>
</tr>
<tr>
<td>Blastocystis hominis</td>
<td>8 of 20 (40.0%)</td>
</tr>
<tr>
<td>Entamoeba coli</td>
<td>2 of 20 (10.0%)</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>0 of 20 (0.0%)</td>
</tr>
<tr>
<td>Hymenolepis nana</td>
<td>0 of 20 (0.0%)</td>
</tr>
<tr>
<td>Giardia sp</td>
<td>8 of 20 (40.0%)</td>
</tr>
<tr>
<td>Ascaris sp</td>
<td>1 of 20 (5.0%)</td>
</tr>
<tr>
<td>Hookworm</td>
<td>0 of 20 (0.5%)</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>0 of 20 (0.0%)</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>1 of 20 (5.0%)</td>
</tr>
<tr>
<td>Taenia sp.</td>
<td>0 of 20 (0.0%)</td>
</tr>
</tbody>
</table>
Cyclospora, or microsporidia. Special requests must be made in order to identify these organisms in submitted stool samples. TMC routinely screens for cryptosporidium only in children under 5 years old.

The discrepancy between the recovery rates in TMC and DLS samples are best explained by the different populations the laboratories serve. Samples submitted to TMC are primarily from military and retired military with dependents who reside in Hawaii. In contrast, the samples from DLS are likely from native residents or from immigrants from other islands in the Pacific.

We are unable to compare the recovery rates of intestinal parasites between Hawaii and non-Hawaii Pacific Islands. However, limited resources in sanitation and medication, as well as the natural presence of these pathogens in developing nations give these regions a relatively high prevalence of intestinal parasites.

Intestinal parasites continue to be a challenge to clinicians in Hawaii. Although the classic pathogens are recovered less frequently, they may continue to be imported by recent or past immigrants. The situation is further complicated by the ability of some parasites to produce no intestinal symptoms and to mimic other diseases for which parasites are not suspected. Patients with acute or chronic intestinal symptoms should be studied for parasite infections as part of a complete work-up. Patients without symptoms who spent significant time in Pacific Islands other than Hawaii also benefit from ova and parasite screening.

Acknowledgments
We gratefully acknowledge the assistance of Mr. Bardwell J. Eberly, Department of Pathology & ALS at Tripler Army Medical Center for his contributions in providing data for this article.

References
Lamivudine Prophylaxis for Chemotherapy Induced Reactivation Hepatitis B: A Case Report and Review

Shane J. Mills MD, Jeffrey L. Berenberg MD, and Fernando Ramos MD

Abstract

Reactivation hepatitis B as a result of chemotherapy induced immunosuppression is well documented in the medical literature. Complications range from anicteric hepatitis to fulminant hepatic failure and death. Although lamivudine has been successfully used to treat hepatitis B reactivation in cancer patients, its role as prophylaxis in these patients is less well defined.

We describe successful lamivudine prophylaxis of a patient with chronic hepatitis B undergoing chemotherapy for acute myelogenous leukemia (AML). We support the position that lamivudine may play a significant role in the successful prevention of reactivation hepatitis B in cancer patients undergoing chemotherapy.

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 U.S. Government.

Introduction

Reactivation hepatitis B in cancer patients undergoing chemotherapy is well documented in the literature. In the setting of chemotherapy-induced immunosuppression, reactivation of hepatitis B can lead to a spectrum of adverse outcomes including fulminant hepatic failure and death. Lamivudine, a reverse transcriptase inhibitor, has been used to treat reactivation hepatitis B in this subset of patients. Although prophylaxis is often suggested, reports are rare. We describe successful lamivudine prophylaxis of a patient with chronic hepatitis B undergoing chemotherapy for acute myelogenous leukemia (AML).

Case Report

The patient is a 25-year-old female with chronic hepatitis B who was diagnosed with AML after evaluation for buccal ecchymosis and extremity hematomas. Initial labs were remarkable for hepatitis B surface antigen (HBsAg) reactivity, hepatitis B virus (HBV) DNA of 0.3 pg/ml, aspartate aminotransferase (AST) of 69 U/L, and alanine aminotransferase (ALT) of 92 U/L.

She began prophylactic treatment with lamivudine prior to induction chemotherapy with idarubicin and cytarabine. Prophylaxis was continued throughout the subsequent consolidation chemotherapy, which included four cycles of high dose cytarabine. Aside from several episodes of neutropenic fever, she tolerated the chemotherapy well. Although the patient had persistently elevated liver associated enzymes (ALT ranging from 68 to 578 U/L and AST ranging from 27 to 180 U/L), HBV DNA levels remained undetectable and the patient had no clinically significant hepatic sequelae.

During her ninth month of treatment, the patient had a prolonged period of pancytopenia with bone marrow biopsy showing a relapse of her AML. After failed reinduction with mitoxantrone and etoposide, the patient was scheduled for an allogeneic bone marrow transplant. At that time, the patient's liver associated enzymes included an AST of 30 U/L and an ALT of 68 U/L. HBV DNA levels were still undetectable. The highest levels of transaminases occurred during induction and reinduction and were thought secondary to chemotherapy-induced hepatotoxicity (Figure 1).

Discussion

A spectrum of liver injury is associated with chemotherapy, ranging from anicteric hepatitis to fulminant hepatic failure and death. Etiologies include viral hepatitis, drug hepatotoxicity, malignant hepatic infiltration, shock, sepsis, and cryptogenic causes. A growing body of literature has concentrated on the adverse outcomes of chemotherapy patients with viral hepatitis.
Reactivation hepatitis B in cancer patients receiving cytotoxic chemotherapy is well reported. Although most cases have involved hematological malignancies (ie, lymphoma), occasional cases involving solid tumors have been reported as well. In a 1991 retrospective study of Chinese lymphoma patients, 27% were found to be HBsAg seropositive. Of these patients, 47% developed reactivation hepatitis during chemotherapy, which resulted in a 5% mortality. In a similar Japanese study, 3.3% of lymphoma patients were found to have chronic HBV infection. Severe hepatitis occurred in 53% of these patients and mortality rates were as high as 24%. In 2000, Yeo et al. conducted the first prospective assessment of HBV reactivation rates in Chinese cancer patients receiving cytotoxic chemotherapy. In this study, 12% of 626 consecutive cancer patients were HBsAg positive, and reactivation occurred in nearly 20% of these patients. This data clearly supports the need for in depth assessment of this adverse process. Of note, hepatitis C infection has also been documented in association with chemotherapy-induced hepatitis, and mortality rates appear to be similar to that seen in patients with HBV reactivation.

There are two proposed mechanisms of reactivation hepatitis B in cancer patients undergoing cytotoxic chemotherapy. The first involves immunosuppression, enhanced HBV replication, and direct hepatotoxicity from infection. The second mechanism involves a rebound immune response upon withdrawal of chemotherapy, resulting in hepatocyte destruction.

Attempts to identify risk factors for reactivation hepatitis B have produced conflicting results. A 1990 study of 105 lymphoma patients by Liang et al. concluded that age, sex, stage, symptoms, lymphoma subtype, presence of hepatic lymphoma, treatment, presence of HBeAg and anti-HBe serologies, and underlying liver pathology were not predictive of hepatic complications. However, a prospective study by Yeo et al. identified several significant associated factors. These included male sex, younger age, presence of lymphoma, chemotherapeutic agent (most common being corticosteroids, anthracyclines, cyclophosphamide, and vinca alkaloids), and HBeAg positivity (although some virulent precore mutant strains are unable to produce the eAg and are still highly associated with fulminant hepatic failure). In our patient, HBVDNA levels remained undetectable throughout chemotherapy, and transient elevations in her liver enzymes were secondary to chemotherapy-induced hepatotoxicity. In a retrospective Israeli study, 13 HBV infected cancer patients were prophylactically treated with lamivudine prior to and following immunosuppressive therapy, with a mean follow-up of 21 months. None of the patients had clinical or serological evidence of HBV reactivation during or after prophylaxis. Likewise, in a prospective Italian study, 20 consecutive patients with HBV and hematologic malignancies were prophylactically treated with 100 mg of lamivudine from the start of chemotherapy until one month after the end of treatment. Only one patient developed reactivation hepatitis during a median follow-up of six months.

Several unresolved issues regarding lamivudine prophylaxis need to be addressed. Specifically, optimal dose, duration of therapy, and resistance have been investigated in chronic HBV patients, but not in those patients undergoing chemotherapy. In a one year trial of lamivudine, Lai et al. showed that 100 mg daily was more effective than 25 mg in the extent of histologic improvement, degree of HBV DNA suppression, and prevention of fibrosis. Duration of therapy and resistance have also been studied extensively, as prolonged lamivudine therapy allows for genotypic mutations in the YMDD locus of HBV that confers a reduced sensitivity to lamivudine. Resistance rates at one, two, three, and four years are 17%, 40%, 55%, and 67%, respectively. These patients typically have higher ALT and HBV DNA levels than those without resistance, but levels on average are still lower in affected individuals than their pretreatment values. Continued histologic improvement is also seen with extended therapy regardless of YMDD resistance, as evidenced by liver biopsies from patients treated with two or more years of lamivudine in the Asian Multicenter trial. In addition, a large co-
hort study showed no increased incidence of hepatic insufficiency or change in adverse events noted with the YMDD mutant HBV. Therefore, while prophylaxis with 100mg of lamivudine for extended periods of time seems safe and effective in chronic HBV patients despite YMDD resistance, randomized double-blinded trials will be needed to better assess these issues in cancer patients undergoing cytotoxic chemotherapy.

**Conclusion**

There are 400 million cases of hepatitis B worldwide with prevalence rates in chemotherapy patients reported at 12%. Reactivation hepatitis occurs in 20-50% of these patients and is a potentially lethal complication, with mortality rates documented as high as 25% in affected individuals. Lamivudine therapy, originally used in HIV patients and then approved for HBeAg chronic HBV, has now been used to successfully treat reactivation hepatitis B in chemotherapy patients. We support the position that lamivudine should also be used as prophylaxis to prevent reactivation hepatitis in cancer patients, and we provide a case report of successful lamivudine prophylaxis.

**References**


On August 1, 2003, sixty-two newly admitted first year medical students marched to the chant of Dr. Kalani Brady, ’82 JABSOM graduate into the auditorium at the Hawaii State Convention Center. The occasion was the “White Coat Ceremony” that welcomed the students into the medical community. Present were family, friends and faculty. Each student was presented a white coat, also called “cloaks of compassion”, by members of the Class of ’82 on the occasion of their 25th anniversary of graduation from JABSOM. In addition, each student received a Stethoscope from the Hawaii Medical Association and Pacific Cardiology, and books, “On Doctoring” from the Robert Wood Johnson Foundation and “Bates’ Guide to Physical Examination and History Taking” from the Friends of the Medical School. The ceremony concluded with the administration of the Hippocratic Oath.

The sixty-two outstanding candidates selected were from 1,284 applicants. Of this number, 256 qualified to be interviewed, 156 in-state and 100 out-of-state applicants. The final roster is made up of 56 in-state and 6 non-residents. Sixty percent are women, the average age is 25, and 24% are reapplicants.

The entering class is ethnically diverse (self-declared) with Mixed/Other Asian 13, White 11, Filipino 9, Japanese 9, Chinese 7, Native Hawaiian/Other 3, Native Hawaiian/ American Indian/ Filipino/Other 1, Native Hawaiian/Samoan/Other 1, Korean 2, Taiwanese 2, Filipino/Japanese 1, Other Pacific Islander/Asian 1, Samoan/White 1., and no response 1.

Twenty-three attended colleges in Hawaii and 39 are from mainland colleges. The colleges include: University of Hawaii at Manoa and Hilo, University of Washington, University of California—Los Angeles and San Diego, University of Southern California, Claremont McKenna College, Cornell University, Occidental College, University of Notre Dame, University of Puget Sound, Brandeis, Brigham Young University—Hawaii and Utah, Chaminade, Christian Brothers, Emory University, Franklin and Marshall College, Gonzaga, Hawaii Pacific University, Loyola Marymount University, Montana State University, Mount Holyoke College, Northwestern University, Pomona College, Rutgers University, Tulane University, University of Massachusetts, University of Michigan, University of Pennsylvania, University of Portland, University of Southern California, Vassar College and Wellesley College.

Over forty-five percent of the class majored in Biology with a combined or minor emphasis in cell and molecular, neurosciences, psychology, chemistry, physiology, public health, and folklore and folk life. Other majors represented are psychology, economics, microbiology, anthropology and human biology, bacteriology, biomedical engineering, chemistry, computer engineering, dietetics, epidemiology, medical technology, Mandarin, nutrition, physics, psychobiology, public health, Sociology, and speech pathology and audiology. All students completed their pre-med science requirements. One student with no Baccalaureate degree was accepted. Eleven students have their masters’ degree and one has a masters and a doctorate.

The median scores for the entering class are: cumulative GPA, 3.63; Science GPA 3.54; MCAT total 28; Verbal Reasoning, 9; Physical Sciences, 9; Writing Sample, O; and, Biological Sciences, 10.

The 11-member Admissions Committee rated all of the 256 interviewed applicants. The Committee was composed of 6 women and 5 men: 8 clinicians, 2 basic scientists and one social scientist who represented the major ethnic groups in Hawaii. This group met 21 times to examine the records of each applicants that consisted of the academic transcript, MCAT scores, essays and the interviewers reports. The applicants were discussed, after which each committee member submitted a secret ballot by rating the applicants from 1-10. The ratings were given to the Registrar who averaged the ratings and set them aside. At the end of April, when all of the applicants had been rated, the applicants were ranked. Fifty-two applicants were offered acceptances. The alternate list was determined by the Dean’s Office. Joining the 52 selected candidates were 9 graduates from the Post-Baccalaureate Program, Imi Ho’Ola. These 9 students completed successfully a year of intensive review of material useful in medical school and prepared to matriculate into the first year.

Sixty-two students with their white coats and stethoscope in hand have begun an exciting journey toward becoming physicians. They are sure to recall the Oath of Hippocrates that they repeated during the “White Coat Ceremony”, “I will remember that caring for the patient will be my primary concern and while doing so I will honor the autonomy of the sick. I will recognize that such caring requires my being available, giving my time generously, communicating honestly, and comforting as well as treating. Such care also involves offering my support to my patients’ loved ones.”

References

1. The Arrow P. Gold Foundation, Inc. 619 Palisade Ave., Englewood Cliffs, New Jersey 07632
Neuroblastoma is a common solid tumor of young children

Neuroblastoma is a childhood cancer originating in pluripotent nerve cells from the neural crest that normally give rise to the postganglionic sympathetic nervous system. It is the most common extra-cranial tumor in infants, with 600 new cases diagnosed in the United States annually. In children neuroblastoma represents 10% of all tumors, but is responsible for more than 15% of pediatric cancer deaths.

One reason for this discrepancy is that in the majority of cases, the tumor has already metastasized by the time of diagnosis. Unlike other forms of childhood cancer, advances in therapy have only recently begun to yield an increase in survivorship for neuroblastoma patients with the more aggressive forms of disease. Since most neuroblastoma patients are infants and young children, the need for less toxic yet more effective therapy is especially important. Some of the major challenges that are being addressed are how to balance the effectiveness of treatment and side effects from radiation/chemotherapy with long-term patient health. New approaches capitalize on the emerging insights we have gained into the biology of this tumor.

Neuroblastoma can regress, or mature to a benign form

One of the most remarkable and unique features of neuroblastoma is the occurrence of complete spontaneous regression, or differentiation. In fact, despite its aggressive behavior in the majority of patients, neuroblastoma exhibits the highest rate of spontaneous regression of any human malignancy. Tumor regression is most commonly observed in infants, while tumors in older patients can differentiate into benign ganglioneuroblastoma or ganglioneuroma. Neuroblastoma thus provides an interesting model system for the development of differentiation therapy that could be less debilitating than conventional chemotherapy, yet increase survivorship.

Retinoic acid turns off the N-myc oncogene, a key step in inducing differentiation

Experimentally, cultured neuroblastoma cells can be induced to differentiate by a number of agents, including retinoic acid, phenylacetate, gamma interferon, and vitamin D. An early, key event in the differentiation process, both in tumor cells exposed to retinoic acid and in normal fetal neuroblasts during neuroanatomical development, is a decrease in N-myc oncogene expression. In turn, N-myc downregulation immediately precedes growth arrest, and is followed by morphologic and biochemical maturation (neurite extension, neurotransmitter biosynthesis, nerve impulse conduction). In patient tumors, activation of the N-myc oncogene is associated with aggressive disease, including tumor metastasis, resistance to chemotherapy, and rapid tumor progression. In the laboratory, if N-myc downregulation is prevented by the introduction of exogenous N-myc genes, retinoic acid-induced differentiation can be blocked. Conversely, decreasing N-myc expression by specific anti-sense oligonucleotides induces tumor cell differentiation even in the absence of any drugs. Thus, regulation of N-myc by agents such as retinoic acid appears to be an important factor in determining the biological behavior of this tumor.

Retinoic acid improves patient survival

Clinically, differentiation therapy with retinoic acid has been shown to have its greatest benefit in the setting of minimal residual disease, following gross tumor debulking by chemotherapy, surgery, autologous stem cell transplant, and radiation therapy. Patients treated with retinoic acid have a significantly higher survival rate than those receiving the same therapy without retinoic acid. With multi-modal conventional therapy, stem cell transplant, and retinoic acid, the current 5-year disease-free survival rate has increased to approximately double that of historical controls.

Retinoic acid resistance is associated with persistent N-myc expression

While new findings on the clinical usefulness of retinoic acid represent encouraging progress, a significant number of children nonetheless suffer from tumor relapse, and survival in patients with disease progression is dismal. Based on cell culture and animal models, a potential cause of failure may be the development of retinoic acid resistance, involving loss of the ability to downregulate N-myc expression.
Understanding the molecular regulation of N-myc transcription

Part of our work at the Cancer Research Center of Hawaii has focused on gaining an understanding of the molecular switch that turns the N-myc gene off in response to treatment with retinoic acid. A decrease in N-myc expression appears to be necessary for differentiation to proceed. Our data suggest that mutations in the control region, or promoter, of the N-myc gene result in the recruitment of alternative transcription factors. N-myc mRNA production is thus driven by a different set of regulatory proteins than in the normal promoter with wild type sequence. Unlike the usual proteins, those associating with mutant promoters may be unaffected by retinoic acid, so that treated cells bearing these mutations can no longer shut the N-myc gene off and continue on with the differentiation program. Persistent N-myc expression, even in the face of retinoic acid, would confer a growth advantage on these cells, and contribute to their chemotherapy resistance. Clinically, such factors may underlie the process of tumor relapse and disease progression.

Clinical applications of mechanism-based research

Through determining the mechanism of N-myc downregulation by retinoic acid we hope to derive a set of molecular diagnostics that will allow us to examine tumor DNA for significant promoter mutations, and use this information to gauge patients' prognoses with respect to their potential responsiveness to retinoic acid. Rather than using retinoic acid as the default drug to deal with minimal residual disease, patients at risk for treatment failure could be triaged to receive new investigative therapies. Identification of the alternate proteins that mediate N-myc transcription in retinoic acid-resistant cells may suggest agents that would be effective even on N-myc genes with mutant promoters. Ultimately these drugs could be used in conjunction with retinoic acid, much like we currently combine different conventional chemotherapeutic agents. However, an important distinction would be that the goal of this combination differentiation therapy would be to effect cure by "rehabilitating" cancer cells, rather than killing them.

Therapy rooted in tumor cell biology, not tumor cell toxicity

Molecular, mechanism-based approaches such as this are part of a newly emerging treatment paradigm rooted in a basic understanding of tumor biology, and should increase treatment efficacy while reducing its toxicity. While this is especially valuable in the therapy of young children, lessons learned in neuroblastoma may one day benefit adult patients with lymphomas and small cell lung carcinomas, since these tumors are also driven by oncogenes of the myc family, including N-myc. For more information, please visit the Cancer Research Center's website at www.crch.org.

References

Even the smallest ads are seen in the Hawaii Medical Journal.
To place a classified ad call 536-7702.
She Is A Vision At Night, But A Sight In The Morning!
The Transportation Security Administration of the government is considering the use of technology called "backscatter" at airport security, which produces a black and white image that reveals all there is to know. All the clothing disappears on the monitor, and only dense materials such as metal or plastic produce a darker image than those deflected off the skin. The agency is working to modify the machines with an electronic "fig leaf" to fuzz out sensitive body parts. A trial project at Orlando in Florida got mixed results from volunteers. Some were uncomfortable and reluctant to be so revealed, but others stated it was a lot nicer than having someone pat them down. Randal Null, the agency's chief technology officer, hopes to conduct some pilot programs this year. Would the backscatter also reveal if Null needs to void?

Perhaps His Purpose In Life Is To Serve As A Warning To Others.
The doctor, a pain management specialist, was called by a patient wanting an injection before leaving for a vacation in Greece the following day. Already booked with a full schedule, the doctor said he would try to work him in. The doctor's morning surgery was prolonged, he had a 25 minute drive to the surgery center where the patient was waiting, and it all added up to a three hour wait for the patient. He sued the doctor for $5,000 to compensate for his waiting time. "They (doctors) have to respect people." It was "unprofessional" and "not nice." Moreover, he claimed the doctor never said he was sorry. Ultimately, a judge awarded the plaintiff $250 in small claims court.

The Fee Will Be Cut In Half, And You Lose Control. Sign Here To Enroll.
It should be no surprise to anyone viewing the Medicaid system that fewer and fewer physicians are willing to care for these patients. In Oklahoma, two doctors and the hospital are being sued because of the death of a five year old girl. Her pediatrician found that she had polyps in her airway, and promptly referred her for surgery. But wait, the pre-op evaluation at the hospital revealed that she had been assigned to a new primary care pediatrician, so the referral was challenged, and the surgery was canceled. In the ensuing delay in seeing her new physician and being referred for surgery, the polyps enlarged, obstructed the airway and the child died. Who gets sued? The doctors and the medical facility are the targets, of course, even though the court records and documents indicate their actions did not cause the breakdown in care. The state Child Death Review Board found that the Medicaid regulations were at fault, and not the doctors. Perhaps the Institute of Medicine, which found so many allegedly preventable medical errors, should look under some Medicaid and Medicare rocks.

Is Doctor Mengele On The Staff, Too?
The question to be answered is how could a physician who had been sued seven times for malpractice, whose license had been suspended in Oklahoma, his application denied in Kansas, and was under review in Hawaii, get any kind of surgical privileges? At some point, one cannot help wondering about the credentialing process at the hospital. In January 2001, this surgeon was performing back surgery and required a titanium rod for a spinal support. Unfortunately, the rod was absent from the surgical tray, and the nurse informed the doctor that one could be flown in from Honolulu, delaying the procedure by 90 minutes. But, the surgeon, being a man of action, could not wait. He picked up a stainless steel screwdriver, saved off a portion, and inserted it in place of the titanium rod. The operating room staff was aghast. A few days later the steel blade snapped, and additional surgery was necessary. The patient became quadriplegic and eventually died from complications of his surgery. This will likely cost Hilo Hospital and the state a bundle.

Astrology Was Invented To Provide Accurate Science For Actuaries.
You could lose what’s left of your patience with Medicare reimbursement, if you tried to understand the accountants and actuaries who decide what doctors should be paid for taking care of America’s senior citizens. Sources within the CMS (once called HCFA) are projecting a range from 0.6% increase to 5.8% reduction for 2004. Rediuction??? Yes, because CMS calculates that if the Gross Domestic Product (GDP) goes down, as has been projected, then doctors will need less money to take care of Medicare patients. This relationship only exists in the minds of lame-brained government actuaries. Congress’ Medicare Payment Advisory Commission (MedPAC) favors a logical system based on providers’ costs and inflation index, and is advocating a 2.5% increase for the coming year. Fat chance! Bush & Co. are busy trying to defend the tax cut and the cost of making war in Iraq, with no indication to see that doctors are treated fairly. When enough physicians opt out of caring for Medicare patients, perhaps the problem will be understood.

Airlines, Yes! Doctors, No!
Right here in our island state, the local airlines, Aloha and Hawaiian, received a sweet exemption from the Federal Trade Commission (FTC) in regard to price-fixing and restraint of trade. And that is why the airlines soon followed with limited and cooperative schedules, and jacked up the airfares. How nice for the airlines. Doctors are treated differently. In Arizona, the FTC lowered the boom on the Carlsbad Physician Association "because the group includes most of the doctors in the area, health plans had no choice but to contract with them." The group will dissolve, the CEO will be barred from other health plan contracting matters, and financial penalties will ensue. This is the sixth time in the last 18 months the FTC has charged a group of doctors with illegal collective bargaining.

Ah, Alcohol! The Cause Of, And Solution To, Life's Many Problems.
Last year Congress directed the National Academy of Sciences to come up with regulatory and policy strategies to curb underage drinking. The 12 member panel is expected to reveal its findings soon which should have significant influence, since the academy is viewed as representative of scientific consensus on issues of public health. People close to the scene think the panel is likely to call for a comprehensive federal strategy including higher excise taxes, limits on advertising, tougher enforcement, restrictions on youth access to alcohol in retail stores, and perhaps a media campaign directed at parents. Lobbyists for the beer and liquor industries argue that the numbers are declining, and that the scope of the study has gone well beyond what Congress intended. They claim the industry is very concerned about underage drinking and spend millions of dollars a year to discourage consumption by youth. They are vehemently opposed to new taxes, advertising restrictions and efforts to limit access in retail stores.

Osama Could Not Begin To Accomplish What We Have Done To Ourselves!
While we taxpayers are seeing billions of our tax dollars each month spread over the middle east to bring democracy to people who don’t seem to want it, and also imperiling our youth. Congress has designated $2 billion for public health “bio-terrorism awareness.” This questionable and foolish, panickey approach allocates funds to stockpile drugs and immunizing vaccines. Meanwhile, state and local agencies are forced to cut funds for schools and local medical clinics. At the same time, Ashcroft and company are tapping telephones, scanning library cards and video rentals, arresting pot smokers, and turning our airports into jammed corridors where the “livestock,” are probed, unshod and forced into a labyrinth of alleys, sometimes ending inside an aircraft. The “war” on terrorism is over – we lost. Whatever happened to those people we sent to Congress to represent us?

ADDENDA
• According to Road and Track, odds that an American driver in a crash will hit a tree are 1 in 95; odds the driver will be a male 9 in 10.
• In millions, the number of cell phones in Japan: 78, in the U.S.: 146, in China: 175.
• Mixing castor oil with holy water will produce a religious movement.
• Scientists claim to have cloned a mule - this is news? I have often made an ass of myself...

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