

# Hawai'i Journal of Medicine & Public Health

**A Journal of Asia Pacific Medicine & Public Health**

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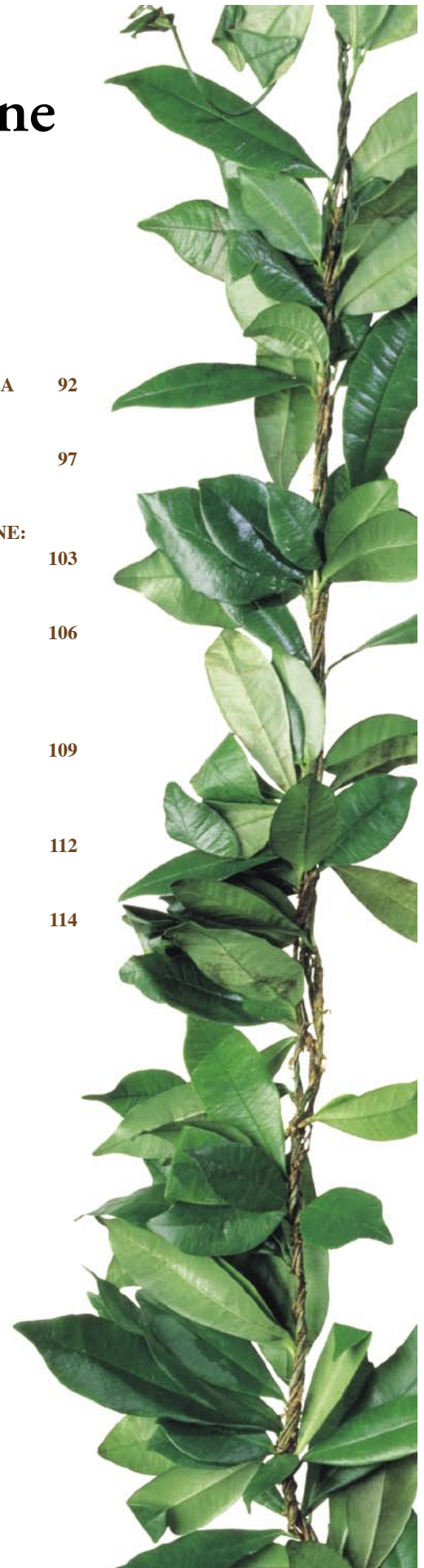
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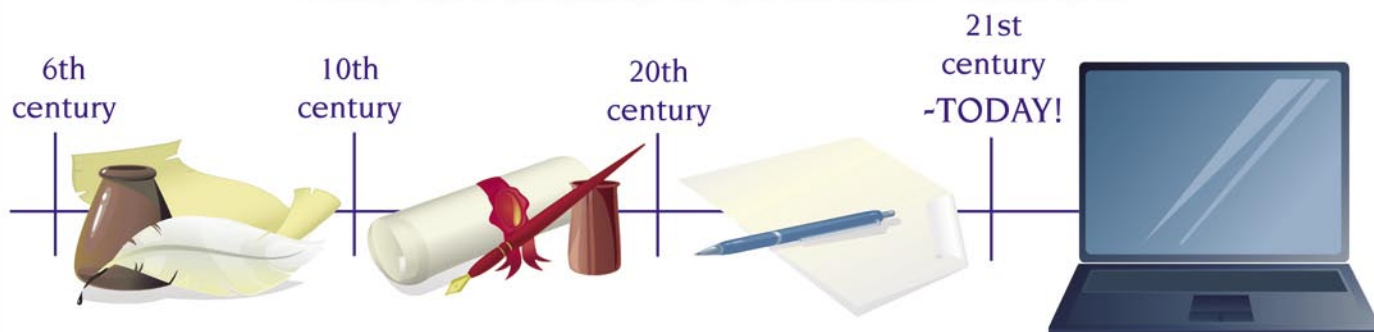
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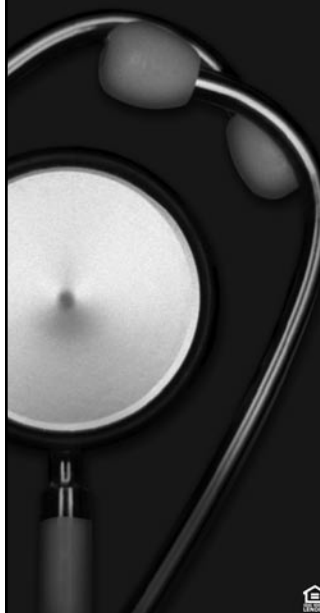
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## Editors' Note:

**As the purview of the Journal expands in content, this is an appropriate time to confirm that we all remain "in touch" with the basic intellectual processes of our profession. We will, therefore, from time to time, solicit and publish specifically labeled review articles covering topics of current interest. Dr. Tabrah's article in this issue is an appropriate beginning.**



# Two Cases of Partial Hepatectomy for Malignant Melanoma

Aaron I. Karlen JD; Justin J. Clark MD; and Linda L. Wong MD

## Abstract

**Background:** While the liver is a frequent site of metastatic spread for malignant cutaneous as well as malignant ocular melanoma, isolated hepatic metastases without evidence of systemic disease is rare. Hepatic resection has been proposed as a therapeutic and potentially curative procedure in metastatic melanoma patients with isolated hepatic metastases.

**Objective:** To report two metastatic melanoma patients with isolated hepatic metastases treated with partial hepatectomy. In addition, the literature is reviewed and the management and efficacy of surgical excision for isolated hepatic disease in the setting of malignant melanoma is discussed.

**Case Report:** A 34-year-old woman with metastatic cutaneous melanoma and a 55-year-old man with metastatic ocular melanoma are presented. Both patients developed isolated hepatic metastases detected during routine surveillance following resection of their primary disease and underwent partial hepatectomy.

**Conclusion:** In select cases, partial hepatectomy is an efficacious and potentially curative treatment for metastatic melanoma patients with isolated hepatic metastases.

## Introduction

Melanoma incidence has steadily increased in the United States, from 14 cases per 100,000 population in 1992 to 19 cases per 100,000 population in 2007.<sup>1</sup> The National Cancer Institute estimates that in 2010 alone, 68,130 new cases of melanoma were diagnosed, with 8,700 deaths.<sup>2</sup> Melanoma is a significant problem in Hawaii, as the state has incidence rates near or slightly higher than the national average at 16.8 to 19.2 and mortality rates of 2.7 to 2.8 per 100,000 population.<sup>3</sup> Compared with other skin malignancies, melanomas more commonly metastasize to local draining lymph nodes and to distant sites such as lung, liver and brain. Metastases can also occur years after initial presentation.<sup>4-6</sup>

The liver is a frequent site of metastases for both cutaneous and ocular melanomas. A study of 216 cutaneous melanoma cases found 58.3% had metastatic disease in the liver.<sup>7</sup> More than 40% of newly diagnosed ocular melanomas have hepatic metastases present at initial diagnosis, and 95% of all ocular melanoma patients with metastatic disease have hepatic involvement at some point in their disease.<sup>8,9</sup> Although hepatic involvement in metastatic melanoma is common, isolated hepatic metastasis is rare in cutaneous melanoma and occurs in about 46% of patients with ocular melanoma.<sup>10-12</sup> Unfortunately, many of these patients are not candidates for surgical resection due to localization or extent of hepatic spread of disease.<sup>11</sup> The infrequency of solitary hepatic metastasis and subsequent treatment provides an opportunity to discuss this rare situation. One patient with malignant cutaneous melanoma and a second patient with malignant ocular melanoma, both with isolated hepatic metastasis, treated with hepatectomy are presented and the literature on this topic is reviewed.

## Case Reports

### Case 1

A 34-year-old woman with a 5.4 cm x 4.6 cm x 2.8 cm deep right arm cutaneous melanoma was treated with wide local excision, right axillary node dissection with 18 nodes negative for metastasis, and 9 months of interferon therapy. A 2.8 cm small bowel metastatic melanoma was resected 5 years later with clear margins. On follow-up 9 months later she was noted on computed tomography (CT) scan to have a 1.4 cm right hepatic mass, that biopsy confirmed to be malignant cutaneous melanoma. The patient received 2 cycles of cisplatin, vinblastine, temozolomide, and high-dose interleukin II as well as 2 cryoablative procedures. However, positron emission tomography (PET) scan showed continued increased uptake in the right hepatic lobe. Abdominal CT scan (Figure 1) and magnetic resonance imaging (MRI) (Figure 2) demonstrated a 4.9 cm x 2.6 cm mass in the right lobe of the liver.

Eighteen months after the initial discovery of the right hepatic mass, the patient underwent exploratory laparotomy with right hepatic wedge resection of segments 4 and 8. A solitary 3.1 cm x 2.7 cm x 2.4 cm metastatic melanoma was resected showing 100% tumor ablation and margins free of disease. The patient recovered well; however, at 6 months after surgery she was found to have a suspicious mass noted in her anteromedial left hepatic lobe and gastrohepatic ligament on PET and CT, later confirmed to be melanoma by biopsy. More than 11 months after surgery, the patient underwent treatment with carboplatin and taxol with little response, and four rounds of ipilimumab with mild response. The patient is currently seeking further treatment options.

### Case 2

A 55-year-old male with Stage III spindle cell B type (fascicular) ocular melanoma of his right eye was treated with right eye enucleation. He did not receive adjuvant therapy and was followed with serial CT imaging. Forty-one months after enucleation, CT demonstrated a 1.8 cm right posterior hepatic lesion in segments 5 and 6. PET demonstrated a 1.9 cm right hepatic lesion with mildly hypometabolic function, without further evidence of metastatic disease. Biopsy showed a lesion consistent with metastatic melanoma.

The patient underwent exploratory laparotomy with right hepatic lobectomy. Pathologic examination grossly demonstrated 2 nodules measuring up to 1.7 cm x 1.5 cm x 1.0 cm within the excised hepatic tissue. Microscopic examination revealed the nodules contained elongated malignant cells arranged in a fascicular pattern associated with melanin pigment, consistent with ocular melanoma (Figure 4). The patient recovered well

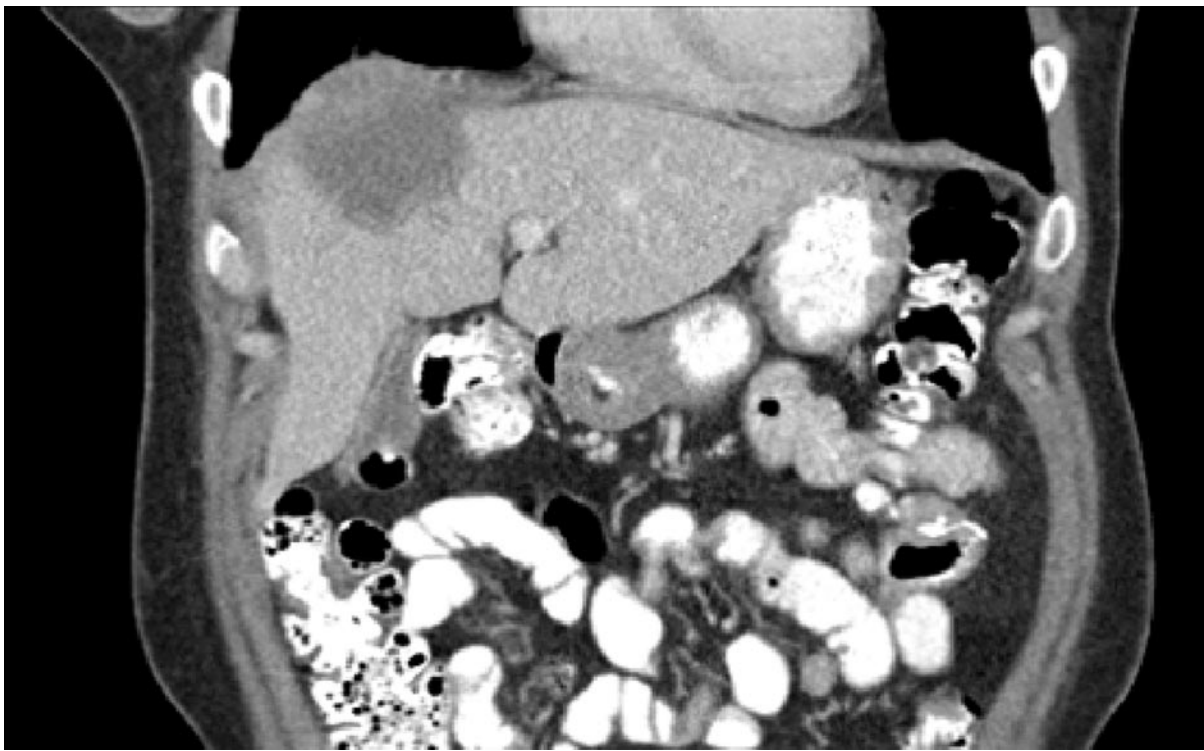


Figure 1. CT Demonstrating Right Hepatic Mass

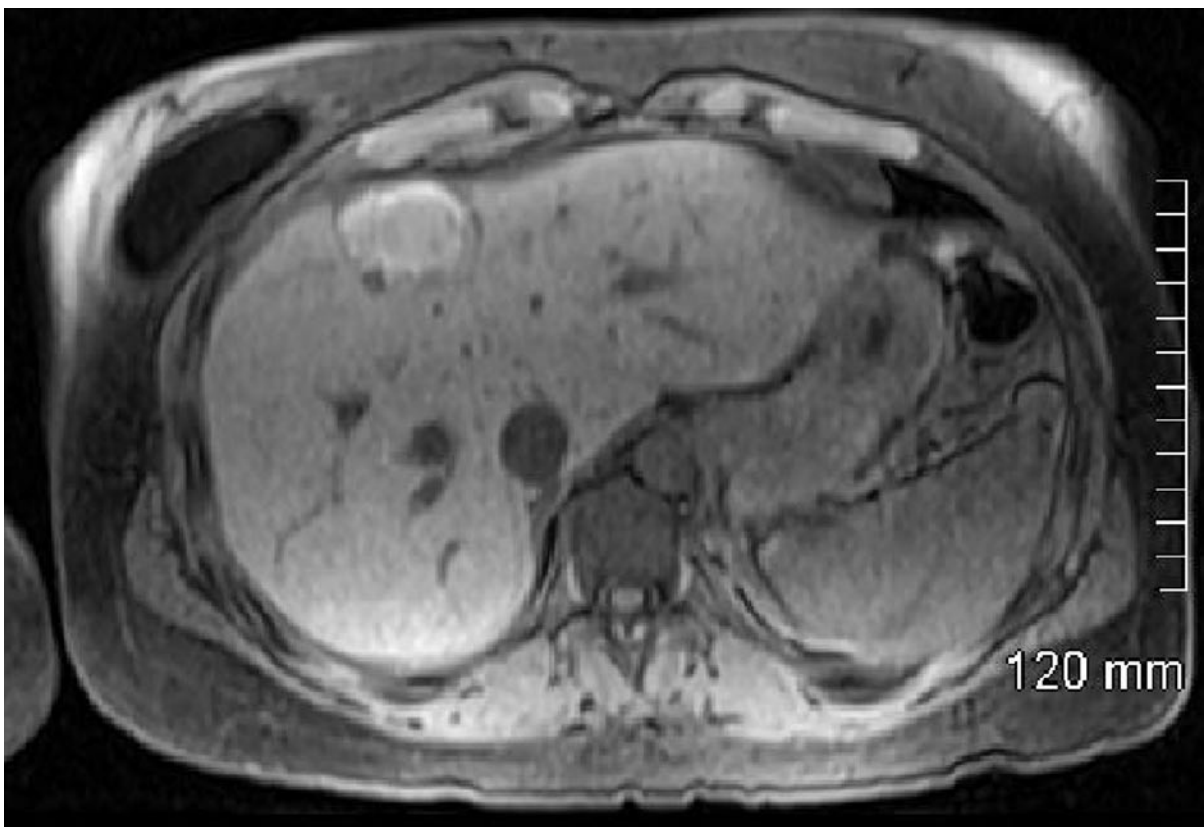


Figure 2. MRI Demonstrating Right Hepatic Mass





Figure 3. 9-Mo. Follow-Up CT Showing Right Hepatic Mass

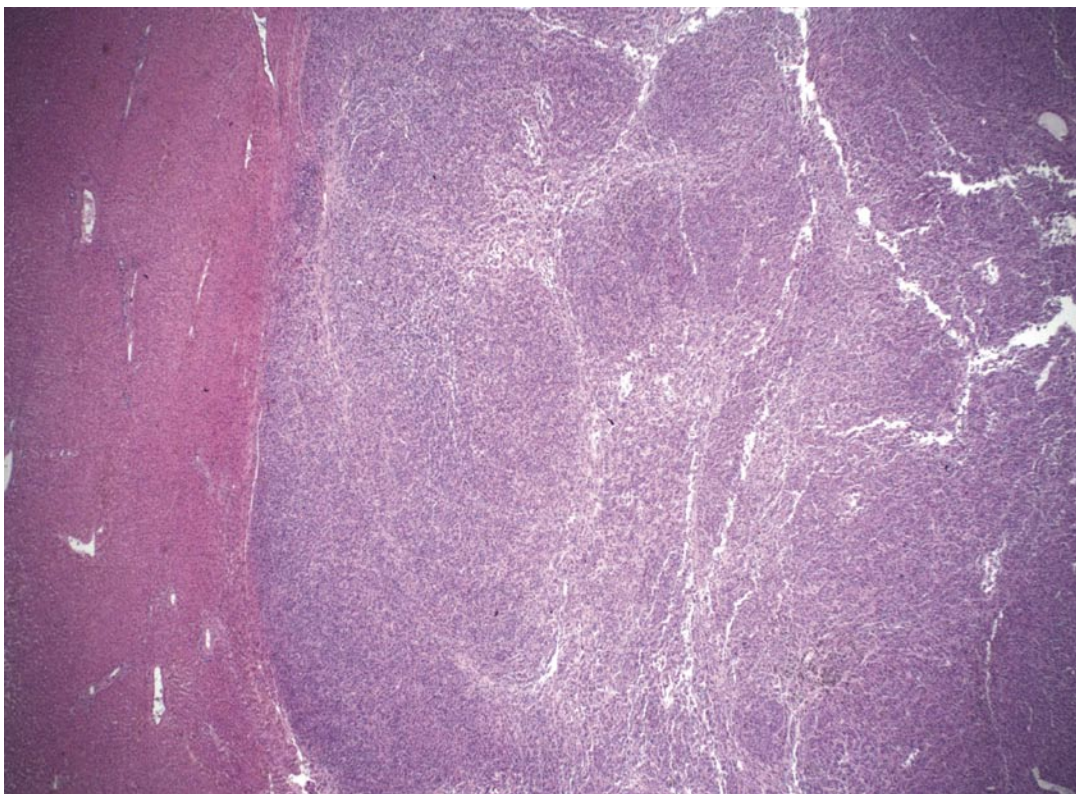


Figure 4. Melanoma & Liver Parenchyma Interface

and had no evidence of disease on PET scan or MRI of the abdomen, neck, face, orbits, or brain 3 months after hepatic resection.

## Discussion

Because melanomas can metastasize long after initial presentation, prolonged follow-up is recommended.<sup>4-6</sup> National Comprehensive Cancer Network (NCCN) guidelines suggest that all patients with melanoma have routine physician follow up, monthly self-conducted skin and lymph node exams, and annual physician skin and lymph node exams for life.<sup>4</sup> NCCN also suggests that patients with melanomas greater than 2 mm or any evidence of nodal or micrometastasis consider follow-up with annual chest X-rays, PET/CT scans, and/or brain MRI, although routine radiologic studies show diminished yield more than five years after initial diagnosis.<sup>4</sup> Although it is well established that surgical resection with or without sentinel lymph node biopsy is the standard of care for primary cutaneous melanoma, there is no consensus for the treatment of metastatic cutaneous melanoma.<sup>13</sup> Similarly, there is currently no effective medical treatment for disseminated malignant ocular melanoma.<sup>9,14</sup>

The liver is a frequent site of metastasis in both malignant cutaneous and ocular melanoma.<sup>15</sup> Classically, median survival after diagnosis of hepatic metastasis has ranged from 2 to 7 months.<sup>8</sup> For cutaneous melanoma, 5-year survival was 3% and median survival in patients with metastasis to the liver was 4.4 months.<sup>16</sup> Survival at 1-year in ocular melanoma with hepatic metastasis is 20%, with 5-year survival of 1%.<sup>10</sup> While the liver is frequently involved with malignant melanoma, hepatic metastasis typically presents with concurrent widely disseminated disease.<sup>11</sup> In these cases, chemotherapy is the treatment of choice.<sup>13</sup> Treatment of hepatic metastatic melanoma with systemic chemotherapy has traditionally yielded a response rate of less than 1%. However, several new molecular-targeted therapies have shown greater success in phase III trials.<sup>9,17,18</sup>

In the case of isolated liver metastasis, treatment options include surgery, chemotherapy, immunotherapy, targeted therapy, surgery, and a variety of other techniques for unresectable disease.<sup>13</sup> Conventional chemotherapy has shown limited efficacy, and sustained remissions are not routinely achieved.<sup>13</sup> Dacarbazine, which before 2010 was the only cytotoxic agent approved by the Food and Drug Administration for treating metastatic cutaneous melanoma, demonstrates objective response rates from 5.5%-20%.<sup>13</sup> Recently, phase III trials have shown efficacy for two novel molecular-targeted therapies.<sup>17,18</sup> A treatment with Ipilimumab, an anti-cytotoxic T-lymphocyte associated antigen 4 antibody, increased median overall survival time of 10.0 months compared to 6.4 months without the drug.<sup>17</sup> Noted to have an immune-related adverse event rate of 10%-15%, ipilimumab was approved by the FDA for use in patients with advanced melanoma.<sup>17</sup> Vemurafenib, a serine-threonine protein kinase B-RAF (BRAF) inhibitor, demonstrated a relative reduction of 74% in the risk of death or disease progression in melanoma patients with the BRAF

V600E mutation, as compared to dacarbazine.<sup>18</sup> Although 38% of patients required dose modification due to toxic side effects, including squamous-cell carcinoma, vemurafenib was subsequently approved by the FDA for treatment of metastatic melanoma with the BRAF V600E mutation.<sup>18</sup> Patients with isolated hepatic metastasis but with unresectable disease due to number or localization of lesions have also been treated with a variety of other methods, including isolated hepatic perfusion, hepatic artery chemoembolization, hepatic artery infusion, and radiofrequency thermal ablation.<sup>11,19</sup> In smaller studies with sample sizes ranging between 19 to 181 patients, these other treatment modalities all demonstrated median survival between 9 and 15 months, except for radiofrequency ablation which demonstrated median survival of 18.5 months.<sup>19-25</sup> Surgical resection has been performed in small studies of selected patients with isolated hepatic and pulmonary metastasis.<sup>11,13,26-28</sup> Surgical resection of isolated hepatic metastasis has recently been demonstrated to achieve local control with improvement of median and 5 year survival.<sup>29</sup>

A review of the literature shows that patients with isolated hepatic metastasis who undergo surgical resection have a median survival ranging from 20-28 months with a 5 year survival ranging from 10.9% to as high as 53.3%, showing a longer median survival than for any other intrahepatic metastasis management technique. In a study of 40 patients with isolated hepatic metastases, 24 of whom had cutaneous melanoma and 16 of whom had ocular melanoma, Pawlik, et al, found that median survival time after hepatic resection was 28.2 months with a 5 year survival rate of 10.9%.<sup>30</sup> Adam, et al, reported a 5 year survival after hepatic resection of 21%-22% in a study of 148 patients, including 44 cases of cutaneous melanoma and 104 cases of ocular melanoma.<sup>31</sup> In a smaller study of 12 patients with ocular melanoma and isolated hepatic metastases, Aoyama, et al, found that surgical excision was beneficial and potentially curative in some cases. While 2 patients had residual disease present soon after hepatic resection, the other 10 patients had a median survival of longer than 27 months with a 5 year survival rate of 53.3%. The 2 patients who had residual disease survived 23 and 25 months post-resection, respectively. Four patients had all evidence of disease eliminated by surgery, although 1 required a second hepatic resection.<sup>29</sup> Several other small studies of 9 to 22 patients with isolated hepatic metastasis from primary cutaneous and/or ocular melanoma demonstrated similar prolonged median survival of 20-28 months.<sup>26,32-36</sup> All of these small trials reported a median survival that greatly exceeded the classic median survival after hepatic metastasis diagnosis.

Our first patient presented with isolated hepatic metastasis from cutaneous melanoma, and our second patient presented with isolated hepatic metastasis from ocular melanoma. Following resection, both patients recovered well and remained disease free for 6 months and 3 months, respectively. Although our first patient had disease recurrence in her liver, she remains active and seeking alternative treatment options more than a year after surgery, a time span already greatly exceeding the 4.4

month median survival for patients with cutaneous melanoma metastatic to the liver. Our second patient is healthy 3 months after surgery and shows no stigmata or sequelae of the resected hepatic disease.

## Conclusion

Melanomas with isolated hepatic metastasis are rare but are more common in patients with primary ocular tumors or larger cutaneous melanoma with nodal involvement. These patients should be followed long-term as metastases can occur many years after resection of the primary tumor. Recommended monitoring includes regular physician follow-up, monthly skin and lymph node self-checks, annual physician skin and lymph node checks, and annual CT, PET/CT, or MRI for more advanced disease. Hepatic resections should be considered in patients with isolated hepatic metastasis, as this can prolong median and 5 year survival, and be potentially curative. Other modalities such as radiofrequency, isolated hepatic perfusion, or chemoembolization may be more appropriate for unresectable liver disease but have not been tested in large groups or compared directly to resection. Systemic chemotherapy, immunotherapy, or targeted therapy should be reserved for patients with disseminated metastatic disease or particular mutation subtypes of melanoma.

## Conflict of Interest

None of the authors identify any conflict of interest or report any financial disclosures.

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# The Care and Feeding of Evidence Based Medicine

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## Abstract

*Wide interest in evidence based medicine (EBM) and its value in patient care, insurance payment decisions, and public health planning has triggered intense medical journal and media coverage that merits review, explanation, and comment.*

*Published EBM data vary in quality for reasons that have been the subject of many perceptive literature reviews. Study design can be faulted, and conflicts of interest, personal and economic, can potentially bias study results and their publication. Practical guides for data evaluation are presented here, with discussion of technical and sociological issues that affect information quality and its clinical application.*

*Clinical practice often appears to resist good evidence in making clinical choices. Personal views of some practicing physicians about EBM are presented that underlie the occasional difficulties in applying valid research information in patient care. Improvements in study design and publication standards may enhance the clinical application of evidence-based information.*

*EBM guided practice holds promise to improve outcomes and expense, to standardize and streamline process in ways that make for much safer patient care.*

Because of recent journal and media attacks on evidence based medicine (EBM) standards and its application, and increasingly complex relationships in the research world, it is timely to review its history, status, public health, and clinical value. How EBM is used in the physician's office, by health officials, and third party payers is critical.

EBM's effect on care access decisions, treatment, and outcomes will largely determine the quality of our health care system. What really works, and what is offered and paid for is of enormous public concern. It is the necessary nidus of resource allocation, the stark reality of all care systems.

Evidence based medicine—exactly what is it? It is use of the best available information in making medical and public health decisions about the care of our patients. Despite its strengths and intellectual appeal, there are serious problems in dependability and its application.

First, its virtues. It is a classic example of Aristotle's logic, the deduction that produces knowledge.<sup>1</sup> Our 21st century application, which we base primarily on peer reviewed literature, began long ago with the reporting of reasonably well controlled two arm studies.

Even before Aristotle, in 600 BC, according to the Babylonian Talmud, David, a foreign youth in training in the king's court, questioned the overrich food the king was feeding him and his friends. He requested a two arm dietary test on himself and his friends, one arm, the king's diet of meats and wine, and the other, vegetables and water. Reportedly, in one arm, health improved on the rigorous diet, and though the trial was underpowered, it remains if true, a 2600 years old attempt at a controlled study.<sup>2</sup>

The author of another early controlled study,<sup>3</sup> was our much maligned Cleopatra Ptolemy who did an experiment on her

maids who had been sentenced to death for various reasons. To determine whether a male and female fetus take the same time to fully develop. She subjected the women to insemination, and at the proper intervals, after their executions, compared their fetal development times. She even controlled for previous palace trysts by administering powerful abortifacients before her timed inseminations, and subsequent slipups by carefully confining her subjects. IRB issues lay 2000 years in the future.

The next well-recorded controlled study<sup>4</sup> was in Holland in 1662. When Dr. Jan Van Helmont arguing against bloodletting, proposed this—and these are his actual words:

“Let us take out of the Hospitals, out of the Camps, or from elsewhere, 200, or 500 poor People, that have Fevers, Pleurisies, etc... Let us divide them in Halfes, let us cast lots, that one half of them may fall to my share and the other to yours; I will cure them without bloodletting and sensible evacuation; but do you do as ye know (for neither do I tye you up to the boasting, or of Phlebotomy, or the abstinence from a solutive Medicine) we shall see how many Funerals both of us shall have: But let the reward of the contention or wager, be 300 Florens, deposited on both sides: Here your business is decided.”

Note the randomization of patient sources and diseases, and that he bet 300 Florins on the outcome—worth sixty thousand dollars in current cash. We must admire his randomization in choosing the patients by lots, his firm outcomes in funeral statistics, and his delightfully innocent wager. Here was a man who clearly enjoyed his work.

From the records of more modern times, it is fascinating to see how long it takes for a convincing clinical advance to affect patient care— and why the delay.

Scurvy was a major killer in historic sea voyages. In 1744, Dr. James Lind,<sup>5</sup> a naval physician, set up this six day experiment: Note the interventions and outcomes, especially # 5.

The trial was done at sea. Twelve patients with severe scurvy were fed identical diets plus supplements in a six arm protocol. The supplements were:

Arms 1. to 6.

1. One quart of cider per day
2. Elix of Vitriol, tid
3. Two spoons of vinegar tid
4. 1/2 pint sea water per day
5. Two oranges and one lemon per day
6. One nutmeg tid

The outcome after this six-day trial clearly showed that the men in arm 5 (oranges and lemons) had recovered and were fit for duty; all the others showed no improvement.

This clear cut result—how quickly was it applied? Through technical problems of preserving fruit or juice, lukewarm inter-



est, and the modest value of dietary onions which were more easily obtained and stored, it was blithely ignored by the entire British Navy, killing sailors for another 48 years until Captain Cook confirmed Lind's work by the use of a daily lime juice supplement for all hands.

Later examples of delayed application of clear data marked the next two centuries. In 1836 when blood letting was rampant, Pierre Louis in France publicized a study, this time testing leeches, in a two arm trial with mortality the endpoint, clearly showing their futility in major diseases. Still, their use was continued unabated throughout the century and well into the 1900s.

Sometimes, new information is even violently resisted. In 1848, Semmelweis, a Hungarian obstetrician faced with many deaths from puerperal fever, showed that hand washing with choline solution reduced an 18% maternal mortality from infection to one percent. His peers, including the great Virchow, fought this for twenty years until Pasteur demonstrated pathogenic bacteria. The fight, in retrospect, was based on the "Semmelweis reflex" a dour historical fact with a new name- that new knowledge is widely rejected simply because it contradicts entrenched norms or beliefs.<sup>6</sup>

Despite the dramatic success of hand washing in his hospital, Semmelweis, for the rest of his life, fought in vain for wide use of his simple life saving intervention. Ignored, he finally went insane, was badly beaten in 1865 by his hospital attendants, suffered a cut finger, and died of septicemia.

On the brighter side, as sound research principles developed, the 1900s saw the triumph of the Patulin study in World War II England, showing the lack of effects of the Patulin mold extract on the common cold.<sup>7</sup> Likewise, the positive Streptomycin studies in the forties proved the immense value of random controlled trials. By then, rational clinical investigation was greatly helped by the development of modern statistics that began in the 1800s and continues today. Here are a few of the pioneers and their contributions:

Bayes and Bayes' Theorem  
Gauss(ian) Distribution  
Wilcoxon test (single t test)  
Mann-Whitney test (unpaired t test)  
Pearson Correlation  
Pearson Chi Square Test  
Spearman Correlation  
Kaplan Meier Survival Curve  
Cox Proportional Hazards, Kendall Tau

Many more can be added—all these efforts fueled the attempts in the early 20th century to strengthen the conclusions of trials by using strict randomization of subjects, and meticulous data collection. Blinding, multiple blinding and other protocol standards soon followed, so today the complexity of a major study can be astounding.

In recent years, results of well-designed studies have made evidence based medicine the holy grail of the clinical and re-

imbursement world. Rightfully, today it guides more and more of our clinical practice and public health efforts.

Despite these developments, clinical practice often appears to resist good evidence in making clinical choices.

The 'Institute of Medicine' has found, that only 4% of our clinical practice is based on evidence from scientific research. In another 45% of cases, there was no evidence used, only a strong consensus among colleagues. And astonishingly in the remaining 50% of cases there was neither evidence nor consensus.<sup>8</sup>

For example, the usefulness of administering corticosteroids to the mother in 'preterm' deliveries for improving lung maturity and preventing mortality of babies from Respiratory Distress Syndrome was established by research in the early eighties. Seven random controlled trials s in 1981 and twelve more in 1990 proved that steroids improved neonatal outcome. Yet by 1994 it was found that only 15% of doctors practiced it, leaving 85% inviting tragic results. Tens of thousands of infants succumbed and millions of dollars were spent on interventions. The wide gap between availability of scientific evidence and its application in practice still persists today. Why?

As in our historic examples, at the physician/patient level, good evidence often clashes with lethargy and freedom of choice. Researchers see it as the road to better care. Some physicians may see it otherwise, citing problems of their status, credibility and economic risk. Even this has been measured. Here are the combined findings of 99 peer reviewed, published physician surveys, collected over the 33 years, 1966 to 199 about their views of evidence based information.<sup>9</sup>

Physicians' perceived limitations included these:

1. Shortage of consistent scientific evidence
2. Difficulties in applying information to the care of patients
3. May preclude practice of high-quality medicine
4. May demand development of new skills
5. Limited time and resources
6. Intellectual "inertia of rest"

Here are some of the physicians' actual quotes:

Evidence based medicine:

1. Denigrates clinical expertise
2. Ignores patient values and preferences
3. Fosters "cookbook" approach
4. Simply a cost-cutting tool
5. Is an "ivory tower" concept

These views have been reinforced by some professional journals and the media.

In 2001 in Greece, a brilliant mathematician and Harvard-trained physician, Dr. John Ioannidis, and his team began a major analysis of the credibility of high level medical research. Their thoughtful conclusions, published in the Journal of the American Medical Association (JAMA) and PLoS ONE (Public Library of Science), led to a hysterical Atlantic article, with

New York Times and worldwide front page coverage, entitled *Lies, Damned Lies, and Medical Science*, which aired Ioannidis' findings, but without the modest reserve of his peer reviewed papers.

However presented, Ioannidis' findings are striking. Based on an analysis of 43 large Random Controlled Trials, published in three leading journals, with over 1000 citations each, and a meta analysis of the findings of subsequent publications, all of comparable quality, here are his conclusions:<sup>10</sup>

One third of the reports of 43 randomly controlled trials were entirely contradicted, or failing effects were found in subsequent studies. In non-randomly controlled trials, five sixths of the original reports were later contradicted.

For example, in 1991, The Nurses' Health Study<sup>11</sup> reviewing estrogen supplementation in women, reported in the New England Journal of Medicine (NEJM) a 44% risk reduction in coronary artery disease. In a total contradiction in 2003 another large trial reported in JAMA, a 29% risk increase.<sup>12</sup>

Similarly, the reports of two very large studies on the effects of vitamin E on coronary artery disease made an interesting contrast; one claimed a 47% risk reduction in infarction or death,<sup>13</sup> the other showed absolutely no effect.<sup>14</sup> These were in Lancet, 1996, and in the NEJM, 2000.

One other interesting study in NEJM,<sup>15</sup> of nine patients in 1993, claimed nitric oxide inhalations were lifesaving in respiratory distress—a metastudy on 539 patients, published by Cochrane in 2003, reported no benefit.<sup>16</sup>

Alarming as these disparities may appear, they illustrate the power of time and accurate reporting of subsequent studies. The publication of conflicting data serves well the intellectual demands of cumulative science. Study conclusions, and treatments, never questioned, can be deadly. The simple passage of time itself can be critical. The thalidomide tragedy is a good example. An airline official once said publically that the real test of a new airliner's safety is the outcome of the first million passenger miles flown. New drugs and devices surely share this analogy.

Recognizing the wide splits in published outcomes data, Ioannidis identifies what he believes to be the main technical issues that impact many studies, generating unreliable information at the highest level of research design, publication, and clinical application. He specifically tags study design technical issues—Recruitment Protocol, Measurement Techniques, Data Selection, and Data Analysis.

Ioannidis and subsequent writers believe these technical faults need to be fixed, and can best be prevented by better trained researchers. Many academic centers now offer six year MD/PhD programs, close Public Health affiliations, and shared expertise with commercial laboratories to improve study design.

Deeper problems, even more difficult, lie in the toxic realm of sociologic (read financial and status) issues. Researchers, peers, and editors are people who live in the real world of clinics and drug companies. All have to eat, and to survive, drug

companies and journals have to make money. Constant attention to the clearly moral issues of research and publication can be difficult and often embarrassing to administrators, research mentors, and editors. Major issues are;

1. Researcher conflict of interest and bias
2. Presentation of results
3. Publication bias
4. Peer review and reviewer relationships
5. Editors' choice of articles to be published (blockbusters)<sup>17</sup>
6. Drug Company relationship to journals
7. Funding sources

These issues, based on status, bias, and money may never be entirely controllable because of powerful conscious and subconscious links in the research and publication chain.

However, improvement may come through the recent attention of universities to potential bias touching on tenure, fame, and money, and particularly, faculty relations with drug companies. Nationwide, Institutional Review Boards' (IRBs') formal requirements for full disclosure of possible conflicts in clinical studies, as well as stringent academic interest in curbing fraudulent research, are certainly positive actions that are being widely applied.

In publishing research, scientifically honest authors must be willing to air important negative trial results which could affect the care of thousands of patients. Medical journal editors of the International Committee of Medical Journal Editors (ICMJE) now require that all clinical trials be entered in a public registry to qualify for publication.<sup>18</sup>

Many conflict of interest concerns have also been addressed by the American Medical Association (AMA). Countrywide, local officers of AMA Facilities Accreditation Committees now mandate broad disclosure statements from all Continuing Medical Education presenters offering accredited programs. Attendees must be routinely asked if they have detected commercial bias in presentations. Commercial bias in a presentation will block its continuing education credit.

In evaluating the complex world of medical information and its dissemination, how can the clinician, the epidemiologist, the peer reviewer, the journal editor, and the public health planner, better weigh the validity of reported outcomes? Some excellent guidelines are available to us for rating the research quality of a study.<sup>19</sup>

Research quality can be rated, according to US Preventive Task Force recommendations, by comparison of study protocols. These step downward in dependability.

- Level I Random Controlled Trial
- Level II Non-Randomized Controlled Trial
- Level II-2 Case Controlled Study
- Level III Combined Expert Opinion

In addition to the study type, in evaluating an article or study report, consider these points:

1. The funding source
2. The authors' credentials
3. The journal's financial support and academic reputation
4. Is the web source commercial or academic?

Important statistical measures in a study are:

1. The likelihood ratio
2. The number needed to treat
3. Specificity and sensitivity
4. "Generalizability" of results
5. Follow-up time
6. Statistical power—very important.

Some excellent sources of EBM information may be found at these addresses:

1. The Cochrane Collaboration (<http://www.cochrane.org>)
2. The Campbell Collaboration (<http://campbellcollaboration.org>)
3. National Guidelines Clearing House (<http://www.guideline.gov>)
4. Ongoing Government Clinical Trials Google
5. AHRQ Outcomes research Fact Sheet Google
6. <http://www.uspreventiveservicetaskforce.org/about.htm>
7. Pubmed
8. [evidenceupdates@mcmasterhkr.com](mailto:evidenceupdates@mcmasterhkr.com)

The Preventive Services URL is likely to be particularly useful to Public Health professionals.

The many publications we are seeing today about Evidence Based Medicine generally agree that despite conflicting outcomes data, the concept is good. In patient care, its values far exceed its limitations as its iterative process operates to improve our interventions.

Some medical insurers fight the cost of new medical procedures and medications by disallowing payment to the point of facing legal action. More enlightened payers have incorporated interventions in clinical practice that save both patients and money.

A striking example<sup>20</sup> of the success of Evidence Based Medicine action based on earlier studies, is the drop of the US colorectal cancer death rate from 28.6 in 1976 to 16.7 in 2007 by two interventions, routine screening and educational efforts to control the risk factors, smoking and obesity. The Kaiser Foundation has been a major player in this outcome, with screening of 75% of its Medicare patients. In forty-nine states, decreased death rates correlate highly with screening and risk factor education.

Two examples<sup>21</sup> in the state of Hawai'i of the use of Evidence Based Medicine to improve patient care, reduce morbidity and mortality, and actually save money were based on literature and national conference information useful to a maternal and child centered hospital.

At Kapiolani Medical Center in Honolulu, in 2007 the incidence of necrotizing enterocolitis in infants born at less than 1500 grams weight was 11%, with 25% mortality. By 2011, care changes, recommended from evidence based studies included trophic feeding with only breast milk, strict transfusion protocols and reduced maternal antibiotics, reduced the incidence of this highly fatal disorder from 9.0 % to 1.8%.

At the same hospital, in 2006, exactly 158 years after Semmelweis, who with solid evidence and little influence preached hand washing in his hospital, Kapiolani staff members decided to curb staphylococcus infections in its infants. Evidence based Mayo and CDC information<sup>22</sup> led to a focused hand washing program for staff and visitors that successfully reduced staph transmission.

The clinical application of information springing from EBM efforts draws on a remarkably wide spectrum of studies, ranging from bench research, through simple clinical observation of a few patients, to massive meta-analyses of outcomes of a specific intervention. Historic examples of clinical advances based on specific laboratory discoveries abound—in the stories of the Koch bacillus, the sulfonamides, and the antibiotics. Other sources of sound clinical information have occasionally come from surprisingly small but definitive studies such as the amusing but highly practical finding of Dr. James Gibson<sup>23</sup> who through a simple study in his general pediatric practice, launched a feeding change that has eliminated, for grateful parents, hundreds of thousands of unnecessary warmings of infant formula for the 85% of American infants partially or totally bottle fed.<sup>24</sup>

Another remarkably simple but critical contribution to EBM came from two practicing physicians in far western Australia, who noted H. Pylori in the stomachs of patients with gastritis and ulceration.<sup>25</sup> A possible causal relationship met widespread disbelief—everyone "knew" that ulcers were stress related. As patients in many studies improved on antibiotic treatment, the import of this discovery led to a Nobel Prize for Marshall's and Warren's insightful contribution.<sup>26-31</sup>

In contrast to these interventions that were based on relatively simple studies, many costly large-scale investigations have been equally successful in providing clinical direction.

The documentation of the overall reduction of ischemic heart disease events by 60% and strokes by 17% by the use of statins lies in the findings of a meta-analysis of 164 randomized placebo controlled trials of six statins and nine cohort studies. The remarkable success of statins in patient care certainly justifies the complexity and costs of these many trials and their analyses.<sup>32</sup>

Evidence based medicine, as well as adding to the treatment armamentarium, can equally well terminate a therapeutic futility. Recently, following the very large PROWESS-SHOCK studies, Drotrecogin Alpha (Activated) or Protein C (Xigris), a medication thought to improve mortality rates of patients with severe sepsis was removed from the market because worldwide trials found that it fared no better than a placebo.<sup>33,34</sup> In this study

involving data from several countries, 1680 severe sepsis patients showed no difference in outcome with or without use of Protein C, resulting in the rational choice of its removal from the market.

In addition to the examples cited, further critical negative evidence based information will be found in a valuable 2011 *Annals of Internal Medicine* article by R. Redberg,<sup>35</sup> summarizing eight more evidence based publications that seriously question current “leading edge” cardiology practices.

Despite these fifteen widely varying examples of EBM clinical interventions, actual access to care and how information is used remain serious problems in the American health system. The application of EBM to patient care encounters powerful human behavior issues. Powerful public response (often irrational) and individual patient preferences can prevail. The public and political response to HPV vaccination, and patient resistance to more exercise and less food despite the obesity epidemic illustrate the stubborn nature of cultural issues. Additionally, as patients compare costs of treatment (or no treatment at all) the bills they face with rising out of pocket costs will certainly affect their outcomes.

Further analyses of the economic and social barriers to acceptance of scientific evidence by care providers, together with better knowledge of actual patient demands will better match interventions with wants and needs. As an example, in a recent *JAMA* article, Detsky<sup>36</sup> offers highly useful information about patients’ clinical expectations that can affect treatment decisions. Such sociologic research should be encouraged to further analyze our ailing health care system, to try to close the gap between our available knowledge and how we use it.

Whether we see health care as a commodity or a right affects clinical outcomes in many settings. Access and payment issues plague the United States, while cultural norms, lethargy and lack of education limit successful intervention in many developing countries. Motivational research can be a valuable informant in putting our clinical concepts to best use. The sociobiologists, behaviorists, and neurobiologists are rapidly adding new insights in human behavior. We should read what they have to say. Much trouble might be spared in the application of new knowledge if we could predict its reception by physicians, patients, and third party payers.

Problems of the resistance to use of evidence bases medicine data in the clinical world may see a partial remedy in the recent development of Translational Medicine programs in major teaching centers. The application of behavioral information gained from the political and social sciences, and particularly, interventional epidemiology, may well be the key to strengthening the use of evidence based medicine in our chaotic world of medicine and its crippled economics. Research and clinical activity demand strong interdisciplinary contact at every level.

Greater interest in the accuracy and application of evidence based medicine is a welcome intellectual response to published outcomes contradictions and the recent upsurge of scientific and medical literature retractions.<sup>37</sup>

Evidence Based Medicine, a prime example of true scientific method, is a progressive collection of knowledge, a self-righting body of information that through the cleansing function of repeated and new studies, gains power in technology and application. Mistakes will still be made in journal articles. Many will be contradicted or corrected in retractions. This is not bad- it is the prime sign of health in the research world that continuously remolds its conclusions.

Research outcomes data are a critical part of this rolling-stone view of science, that is best seen with the optimistic mindset that most medical information published in established peer reviewed journals is valid until proven otherwise with better data- a useful bedside philosophy.

## Conflict of Interest

The author reports no conflict of interest related.

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# An Incidentally Discovered Left Atrial Appendage Membrane: Case Report and Literature Review

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## Abstract

*The left atrial appendage (LAA) is an extension of the left wall of the atrium and its close anatomic relationship to the free wall of the left ventricle gives it anatomic characteristics distinct from the left atrium. To date, only seven cases involving a LAA membrane have been described. A patient with an incidentally discovered, partially obstructive membrane at the orifice of the LAA, causing functional stenosis is presented, and our case is compared to those in the existing literature.*

*The clinical significance of LAA membranes remains unknown. These rare membranes are usually an incidental finding on transesophageal echocardiogram during evaluation of an atrial dysrhythmia. It is not clear if these membranes could be promoting atrial fibrillation or if the association is merely a result of sampling bias. These membranes may also affect cardioembolic risk. Finally, the increasing use of percutaneous catheter-based therapies such as radiofrequency ablation and occlusion of the left atrial appendage, will likely result in the increasingly frequent identification of these membranes, and when present may increase the technical difficulty associated with these catheter-based therapies.*

## Keywords

*left atrial appendage; anomaly; membrane; transesophageal echocardiography*

## Introduction

The left atrial appendage (LAA) is an extension of the left wall of the atrium and its close anatomic relationship to the free wall of the left ventricle gives it anatomic characteristics distinct from the left atrium. Membranes in the left atrial appendage are very rare. Only seven cases involving a LAA membrane have been described. This instance of an incidentally discovered, partially obstructive membrane at the orifice of the LAA, causing functional stenosis, is compared to those in the existing literature.

## Case Report

A 26-year-old man with no significant medical history was referred to our institution for a single symptomatic episode of exercise-induced atrial fibrillation. He denied alcohol use. Serum electrolytes and thyroid stimulating hormone level were normal. Transthoracic echocardiogram and graded exercise treadmill test were normal. A transesophageal echocardiogram (TEE), ordered to assess the risk of thromboembolic stroke in lieu of four weeks of anticoagulation, demonstrated a thin, immobile, partially obstructive membrane separating the left atrial appendage from the cavity of the left atrium (Figure 1). A single 1 mm orifice provided direct communication between the cavities. A well-defined jet emanated from the LAA into the left atrium during atrial systole, suggestive of a significant pressure differential between the two chambers. There was no evidence of thrombus. Cardiac magnetic resonance imaging (Figure 2) confirmed the presence of a partially obstructive membrane

across the opening of the left atrial appendage (Video 1). The patient underwent successful cardioversion without recurrence of his atrial fibrillation.

## Discussion

The clinical significance of left atrial appendage membranes remains unknown. Atrial dysrhythmias were present in four of the seven cases in the literature, and two cases presented with stroke. Although not all of the patients demonstrated atrial fibrillation or flutter, all had clinical conditions in which atrial fibrillation was more likely, such as left atrial enlargement and embolic stroke with an unknown source.<sup>1-3</sup> When found, LAA membranes are usually an incidental discovery on TEE during evaluation for an atrial dysrhythmia or stroke. There are five described cases of nonobstructive membranes traversing the body of the left atrial appendage: three occurred in the setting of atrial fibrillation, one occurred with atrial flutter and one presented with stroke one month after a three-vessel coronary artery bypass surgery and biologic aortic valve replacement.<sup>1,4,5</sup> In addition, two cases described a nonobstructive membrane across the opening of the left atrial appendage. The first was incidentally discovered on TEE along with left atrial enlargement during evaluation of dyspnea/shortness of breath. Ultimately, the patient underwent a mitral valve replacement and left atrial appendectomy.<sup>2</sup> Another patient presented with a transient ischemic attack.<sup>3</sup> In addition to these spontaneous cases, there are also cases of failed surgical ligation of the LAA that were discovered to have a functionally similar stenosis of the LAA opening due to incomplete ligation discovered during work up of atrial dysrhythmias that began after surgery.<sup>6</sup>

The origin of these membranes is unknown, but they are likely a congenital anatomic variation. These membranes have been described in older adults with no history of prior cardiac surgery, suggesting a congenital etiology.<sup>1-4</sup> The clinical significance of these partially obstructive membranes is not clear. It is unknown how these membranes affect cardioembolic risk. Stagnant flow within the LAA membrane may predispose to thrombus formation while the membrane itself may decrease the risk of systemic embolization, or at least limit the size of emboli. In addition, it is unclear to what extent these membranes may be playing a role in promoting atrial dysrhythmias or if the association is merely a result of sampling bias. The LAA is thought to modulate the pressure and volume in the left atrium, and loss of this physiologically distensible cavity may worsen left atrial pressure and volume overload, increasing the risk for atrial dysrhythmia.<sup>2</sup> Finally, the increasing use of percutaneous catheter-based therapies such as radiofrequency ablation and occlusion of the left atrial appendage will likely result in the

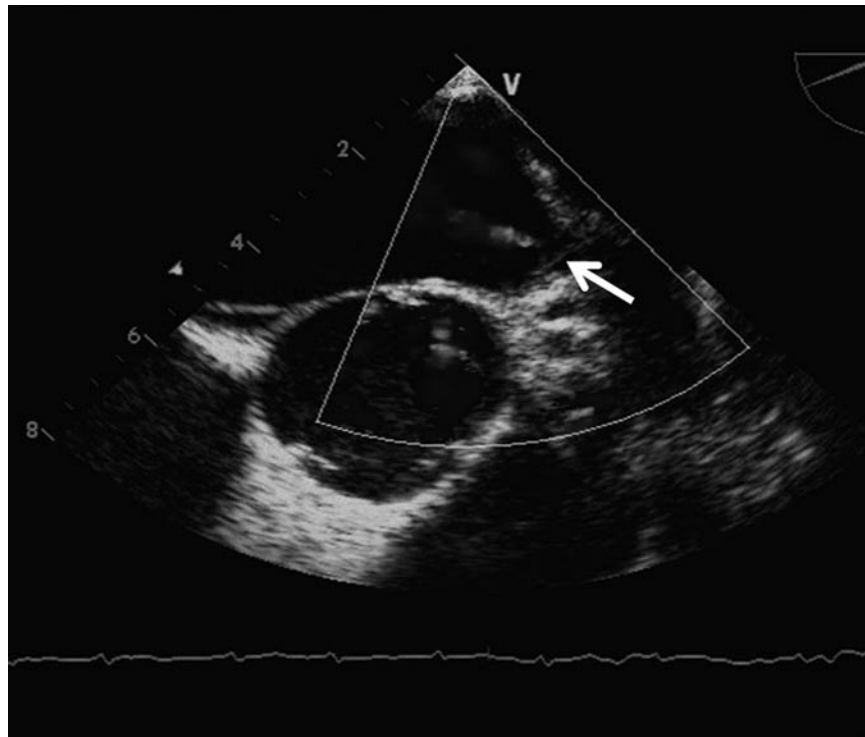


Figure 1. Transesophageal echocardiogram still image demonstrating the left atrial appendage membrane with a jet of flow exiting the orifice in the membrane into the left atrium (membrane and source of jet are indicated by the arrow).

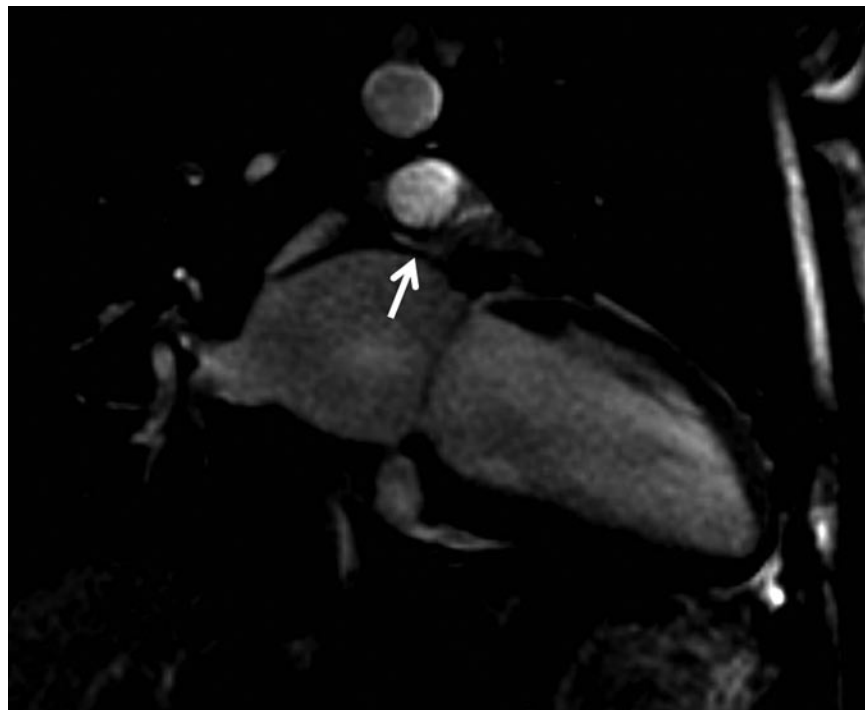


Figure 2. Cardiac MRI image that demonstrates contrast filling the left atrial appendage. The arrow indicates the location of the LAA membrane, which appears black, causing a functional stenosis at the opening of the LAA membrane.

increasingly frequent identification of these membranes, and when present may increase the technical difficulty associated with these catheter-based therapies.

This left atrial appendage membrane is a distinct entity from cor triatriatum sinistrum, which is a congenital intra-atrial membrane that usually separates the superior and inferior portions of the primary left atrium. The membrane found in our patient is in the left atrial appendage, which has developmental and physiological characteristics distinct from the main left atrium. The left atrial appendage is the remnant of the original embryonic left atrium that develops during the third week of gestation; the main left atrium develops later from the outgrowth of the pulmonary veins.<sup>7</sup> Thus, the origin of the left atrial appendage membrane found in our patient is likely unrelated to a cor triatriatum.

The authors describe a rare membrane at the opening of the LAA, incidentally found on transesophageal echocardiogram, which is not easily assessed by any other imaging modality and may play a role in promoting atrial dysrhythmias, affect cardio-embolic risk and complicate some catheter-based therapies.

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

### Disclosure Statement

The authors have no disclosures. None of the authors identify any conflicts of interest.

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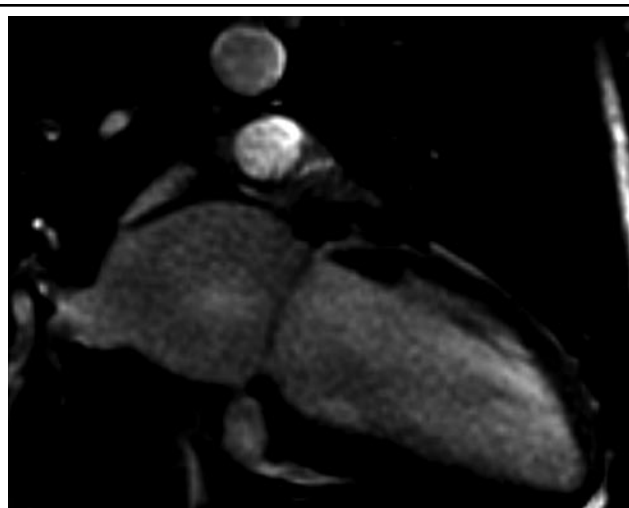
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Still image of Video 1 above. Video taken from the cardiac MRI cine sequences demonstrating the presence of a membrane at the opening of the left atrial appendage, with a well defined jet emanating from the LAA into the left atrium during atrial systole, suggestive of a significant pressure differential between the two chambers.

(To see Video 1 go to — <http://www.hjmph.org/smithvideo1.htm>)

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## PUBLIC HEALTH HOTLINE

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### **The Doctorate in Public Health (DrPH) in Translational and Community-Based Research at the University of Hawai'i at Manoa**

**Kathryn L. Braun DrPH; Professor and Chair, DrPH Program, Office of Public Health Studies,  
John A. Burns School of Medicine, University of Hawai'i at Manoa**

The Doctorate in Public Health (DrPH) program in the Department of Public Health Sciences (DPHS) at the University of Hawai'i at Mānoa prepares students for academic and leadership positions in public health. Students gain qualitative and quantitative research skills to answer research questions relevant to culturally diverse groups, especially those in the state of Hawai'i and the Asia-Pacific region.<sup>1</sup>

The program has five goals. First, we aim to provide students with a multidisciplinary perspective inherent in public health. Second, we prepare students for independent inquiry in public health, with a focus on translational and community-based participatory research that addresses issues of concern to culturally diverse groups. Third, we prepare students for leadership roles in evidence-based public health and health-disparity reduction. Fourth, we strive to increase the number of professionals, especially in Hawai'i and the Pacific region, who are qualified to conduct independent public health research, to teach, and to lead the practice of public health. Finally, we hope to increase the number of doctorally trained public health practitioners from under-represented groups.

#### **Research to Practice**

Our DrPH Program focuses on translational research, and we emphasize community-based participatory research methodologies, reflecting our commitment to working in partnership with communities to recognize, quantify, and reduce health disparities. In the context of public health, translational research is the investigation of how to successfully transform scientific discoveries arising from laboratory, clinical, or population studies into community applications to reduce incidence, morbidity, and mortality of diseases. The National Institutes of Health and others agree that we must "close the gap" between research discovery and program delivery if we are to ensure that all populations benefit from the nation's investments in new scientific discoveries.<sup>2,3</sup> Translational research includes "dissemination and implementation research," which explores how we can effectively disseminate information about and replicate successful evidence-based programs in community, public health, and clinical practice settings.<sup>4,5</sup>

Community-based participatory research (CBPR) in health is a collaborative approach to research that equitably involves community members and investigators in the research process and recognizes the unique strengths that each brings.<sup>6,7</sup> CBPR

begins with a research topic of importance to the community and has the aim of combining knowledge with action to achieve social change to improve health outcomes and reduce health disparities. Health disparities refer to significant differences in the incidence, prevalence, mortality, burden of diseases, and other adverse health conditions or outcomes that exist among specific population groups. For example, in the United States, many immigrant and minority groups have higher prevalence of chronic diseases, less access to healthcare, and lower life expectancy than Caucasian Americans.<sup>8</sup> The existence of health disparities in Hawai'i is well illustrated by large differences in life expectancy by ethnicity. In 2000, life expectancy for Chinese residents was 86.1 years, followed by 82.8 years for Japanese, 81.4 for Korean, 80.9 for Filipino, 79.0 for Caucasian, 74.3 for Hawaiian, and 72.8 for Samoan residents (a startling 13 years shorter than for Chinese).<sup>9</sup>

#### **Aligned with University of Hawai'i (UH) Values of Social Justice and Place**

The DrPH program was designed to closely align with the mission and strategic plan of the University of Hawai'i at Manoa, as it addresses the core commitments of the University in research, educational effectiveness, social justice, and place.<sup>10</sup> The DrPH focuses on translational community-based research, ie, developing, testing, and improving interventions that reduce incidence, morbidity, and mortality of diseases, especially in communities that experience health status and health access inequities. Emphasis is placed on community-based participatory methods that engage community members in research processes, which increases the chance that interventions will be embraced by the community and that community members will gain knowledge, skills, and other benefits from the research. The curriculum focuses on developing public health leaders from Hawai'i, the Pacific, and Asia and supporting research relevant to the people and cultures of this region. A broad social justice perspective assures that skills can be applied to any community or group experiencing health disparities.

The DrPH faculty includes professors and researchers from the Office of Public Health Studies, other departments in the John A. Burns School of Medicine (JABSOM), the UH Manoa campus, the UH Cancer Center, and the Hawai'i Department of Health. All members have active programs of research, with funding from the National Institutes of Health, other federal

agencies, private foundations, international funders, and local government. All members have significant records of peer-reviewed publications and academic presentations. Three have won university-wide teaching awards.

### **Coursework and Milestones**

To encourage students in original and independent scientific thinking and public health practice, the faculty provides a balance of intensive guidance (eg, through regular assessment and feedback) and freedom for students' own ideas and projects. Entering students should have a Masters in Public Health (MPH) or have completed public health courses in social science theory, program evaluation, epidemiology, biostatistics, and research methods.

Once in the program, students take courses in health disparities, evidence-based public health, cultural competence, leadership, policy, community-based participatory research, qualitative and quantitative research methods, multivariate analysis, and their individual areas of specialization. All DrPH students complete a mentored teaching practicum, which includes co-teaching with a seasoned faculty member, providing lectures, and evaluating student work. They also develop curricula and prepare written explications of their teaching philosophy. In the research practicum, each DrPH student is partnered with a senior scientist working in the student's research interest area. The work often entails secondary data analysis, and the team is encouraged to publish the findings. Over the course of the program, each student prepares a portfolio of scholarly products and achievements, including a systematic literature review, research proposals, policy analysis and advocacy pieces, publications, conference presentations, and products from the teaching practicum.

Students transit through three phases. The Qualifying Phase includes the first year or two of coursework. It culminates in the passing of a qualifying exam and the writing and presentation of a qualifying paper, usually a systematic review of the literature in the area of the student's interest. During the Specialization and Practice Phase, the student completes coursework, including the teaching and a research practica, and prepares his/her dissertation proposal. This phase concludes in the successful defense of the proposal and the passing of the comprehensive exam. The final phase is the dissertation research and the successful defense of the dissertation. Full-time students should be able to complete the DrPH in four years.

### **Dissertations that Promote Community Health and Publication**

Students are encouraged to pursue dissertation research that will answer questions of importance to their community of interest. But we also recognize that graduating students need a competitive edge, and that early publications will contribute to future success. Thus, the DrPH Program requires a three-paper dissertation format, rather than the more common book format. Each of the three papers explores a research question relevant to the overall dissertation topic. The final product includes an

overview, three manuscripts of publishable quality related to the central theme of the dissertation, and a conclusion suggesting future directions for research, practice, and policy. At least two of the three manuscripts must be based upon empirical research conducted by the student, and one must report on a study using qualitative methods and the other on a study employing quantitative methods. The third manuscript may be non-empirical, for example a systematic literature review or a policy analysis. Provided below are examples of the DrPH dissertation from three students that graduated in 2011. Each has already submitted two of the three dissertation papers for publication.

#### **Research to Understand and Prevent Youth Violence**

Recent graduate, Jane Chung-Do, focused on youth violence prevention. Working through JABSOM's Department of Psychiatry, she partnered with a local high school to examine the influence of school connectedness on interpersonal youth violence prevention with a focus on Asian and Pacific Islander youth. For her first paper, she conducted focus groups with high school students to understand their perceptions of a high school course designed to enhance school connectedness. Findings suggested that teacher support plays an essential role in students' perceptions of the course effectiveness.<sup>11</sup> Her second paper reported on the psychometric properties of a scale she developed with the high school teachers to measure school connectedness. Findings revealed that school connectedness is a multi-dimensional construct. Her third paper reported on an examination of the associations between violence and school connectedness using structural equation modeling, which found that school connectedness is an independent protective factor for interpersonal violence.

#### **Research to Improve Samoan Health**

Another recent graduate, Kevin Cassel, worked with the Samoan community in Hawai'i to explore if and how "Body and Soul," a church-based, evidence-based, health promotion program successful in African-American communities, could be tailored for replication in Samoan churches. His first paper was a systematic literature review using the social-ecological model as a research and intervention framework to understand and mitigate obesogenic factors in Samoan populations.<sup>12</sup> His second paper reported findings from key informant interviews and focus groups with Samoan community and church members about the types of health-promoting interventions that might appeal to Samoans and the best setting for such an intervention. Findings suggested that the church was a preferred setting for health-related interventions, and that Body and Soul would be replicable if tailored to the Samoan community. For his third study, he conducted a secondary analysis of dietary data obtained from more than 1,400 Samoans living in American Samoa, Hawai'i, and California. Findings identified dietary consumption patterns specific to Samoans that can be promoted, including fish, fruit and vegetable patterns, or discouraged, such as consumption of high fat meats, white rice, and processed traditional and Western foods. This information also proved

useful in the development of brief dietary assessment instruments to measure the effectiveness of interventions, like Body and Soul, with this population.

### Research to Improve Breastfeeding Rates

Kristen Mitchell-Box, a third recent graduate, focused her dissertation on the role of the male partner in supporting breastfeeding. An exploration of this topic was of great interest to Hawai'i providers of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), with which Kristen, a certified lactation counselor, volunteered. Her first study was a systematic literature review of educational interventions for male partners. Only ten such interventions were found, and this paper provides recommendations for future programming and research. The second paper reports on a qualitative study of male partners accompanying new mothers to WIC appointments, which found that fathers supported breastfeeding conceptually, but did not know how to help facilitate it and were embarrassed by breastfeeding in public, suggesting areas that would need to be covered in an intervention.<sup>13</sup> For her third study, she administered a 5-minute breastfeeding attitude scale with both mothers and fathers. Total scores were predictive of intent to breastfeed, and mother's and father's scores were highly correlated. If used as an assessment tool, scores could help identify women and partners with negative attitudes and misconceptions who would benefit from an intervention to increase breastfeeding initiation and duration.

### Conclusion

We believe that the DrPH program builds strong public health leaders for Hawai'i and the Asia/Pacific region. DrPH students are trained in both qualitative and quantitative methods so they can best help communities examine research questions of interest to them. They are committed to translating scientific discovery and replicating evidence-based programs to our communities with the aim of reducing health disparities. For more information on the program, visit the University of Hawai'i Office of Public Health website: [www.hawaii.edu/publichealth](http://www.hawaii.edu/publichealth).

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## MEDICAL SCHOOL HOTLINE

SATORU IZUTSU PHD, CONTRIBUTING EDITOR

### Hyperbaric Treatment Center of the University of Hawai'i: 2012 Update

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Diving Medical Officer; Director, Office of Student Affairs, John A. Burns School of Medicine;  
and Frank Farm Jr.; Director Hyperbaric Treatment Center**

The Hyperbaric Treatment Center (HTC) of the University of Hawai'i, John A. Burns School of Medicine provides vital services for the citizens of Hawai'i as well as countless visitors. Established in 1983, the HTC assumed responsibility for the treatment of diving related casualties which had been previously attended to by the US Navy at Pearl Harbor. Seeing the increasing need for such services, then Governor George Ariyoshi, with appropriations provided by the state legislature, established a planning group to develop and build the HTC.

Initially, the chamber was located at Kewalo basin. The facility was relocated to Kuakini Medical Center in 1995 where it now resides. This modern facility has three multiplace recompression chambers and is one of only a very few chambers in the United States capable of treating with mixed gases as needed. The essential mission of the HTC is to be available and capable of treating victims of decompression illnesses (DCI) 24/7. Led by Dr. Ed Beckman and Frank Farm, the unit took form, developed treatment protocols; trained staff; co-ordinated with other agencies including the US Navy, Coast Guard, Honolulu Fire Department, and EMS for emergency evacuation; and created appropriate contact and referral mechanisms to provide expeditious critical care to injured divers. Currently, nearly 30 years since its founding, the HTC enjoys a reputation for excellence in the management and treatment of diving accidents, not only locally, but also nationally and internationally. It is one of only 116 hyperbaric facilities within the United States to have been accredited by the Undersea and Hyperbaric Medical Society, a Joint Commission on Accreditation of Healthcare Organizations level inspection for hyperbaric facilities aimed at insuring that the program meets the established standards of practice and quality care, maintenance of equipment, professionalism, administration, operations, safety, clinical research, teaching, and publishing. It is the only accredited chamber in the state of Hawai'i.

The Center is staffed by four physicians, three of whom are board certified in the subspecialty of Undersea and Hyperbaric Medicine and hold a clinical faculty appointment in John A. Burns School of Medicine's Department of Surgery. Collectively, these physicians have over 65 years of combined diving medical practice and expertise. In addition, the HTC is staffed by a registered nurse, four hyperbaric technicians, and on-call technicians all trained in a National Board of Diving and Hyperbaric Medical Technology approved course.

The HTC has been designated as the Pacific Regional Co-ordination Center for the Diver's Alert Network (DAN) to provide assistance to injured divers throughout the Central Pacific region. More than 1600 divers have been treated to date. Ninety-three percent of those treated obtained full recovery upon completion of treatment. About one half of those treated have been tourists to the islands.<sup>1</sup> Most of the patients with diving accidents were treated using the "Hawaiian Deep Tables" developed by Dr. Beckman at the HTC specifically for divers with extended delays to treatment and for whom the US Navy treatments had not been successful. These unique treatment tables consist of an initial deep spike to as deep as 220 feet of seawater (fsw) pressure followed by a modified version of the US Navy treatment table at 60fsw pressure. Their implementation and usage have improved recovery rates from 59% to 93%. This latter outcome rate is 20% better than that reported as a national average.<sup>2</sup> In addition, the HTC provides invaluable medical advice and expertise to support the scientific diving operations and Diving Control Board of the University of Hawai'i, NOAA, and the Bishop Museum, as well as for diving operations of the Department of Land and Natural Resources, the Honolulu Fire Department, and commercial diving activities.

The HTC also treats patients who have medical conditions that are amenable to hyperbaric oxygen (HBO) administration. These applications are approved by the Undersea and Hyperbaric Medical Society (UHMS) based upon substantiated scientific evidence. Conditions considered are: carbon monoxide intoxication, clostridial myonecrosis (gas gangrene), necrotizing soft tissue injury, delayed radionecrosis, acute blood loss anemia, enhancement of healing of problem wounds, preservation of compromised skin grafts and flaps, acute traumatic ischemias, refractory osteomyelitis, intracranial abscess, and thermal burns. In the past two years the Hyperbaric Oxygen Committee of the UHMS approved the use of hyperbaric oxygen for the treatment of central retinal artery occlusion and idiopathic neural sensory hearing loss. Since 1983, over 900 patients have been treated with HBO for a total of 16,000+ treatments. The majority of these cases have been treated since 2000 due to the increased awareness by the general medical community of the benefits of HBO as adjunctive treatment for certain conditions.

Historically, the most common use of HBO, nearly 66% of the cases at the HTC, has been for radiation related damage resulting from radiotherapy. In 2007, the HTC received a Cer-



tificate of Excellence from the American College of Hyperbaric Medicine for its contribution to establishing a national registry of patients treated with HBO for radionecrosis. The second reason for which HBO is sought is that of non-healing diabetic wounds of the lower extremity. With the ever-increasing number of those diagnosed with diabetes in the state,<sup>3</sup> it is anticipated that the incidence of diabetic wounds will increase resulting in a greater demand for HBO to aid in wound healing and potentially increase limb salvage.

As a university based entity, the clinical faculty is engaged in various academic pursuits. Over the past decade, the staff has taught and trained over 1000 residents and medical students in Undersea and Hyperbaric Medicine. Many of these residents were Emergency Medicine residents who came to Hawai'i from the mainland specifically to obtain this training. The HTC is uniquely suited to provide education and experience in the field of Undersea and Hyperbaric Medicine. It is one of only a few facilities in the United States which conducts diving medical research. Since 2001 the HTC faculty's clinical research projects have resulted in 18 papers and 29 abstracts published in peer-reviewed journals. The staff has made 45 formal presentations at scientific meetings and symposia in the US, Australia, and New Zealand.

Among these publications there are several "firsts" in the literature:

- (1) In 2004, the HTC demonstrated that there was a gender disparity in tolerance to high dose oxygen in divers treated for decompression illness. Women were more adversely affected by oxygen toxicity;<sup>4</sup>
- (2) The HTC reported on the epidemiology and treatment of decompression illness sustained in children and adolescent divers;<sup>5</sup>
- (3) The HTC reported on the epidemiology and treatment of a large series of divers who presented with pure isolated inner ear decompression sickness;<sup>6</sup>
- (4) A recently completed study (submitted for publication) is the first to investigate the association of the use of a particular drug class while diving and the risk for developing the bends.<sup>7</sup>

The HTC has also collaborated with research institutions in the United States, Europe, Japan, and Australia in diving research efforts related to women and diving, enhanced diving injury data collection and analysis, and flying after diving. While diving research has remained the primary focus for publication, the HTC staff has also published on topics concerning HBO treatment.<sup>8-10</sup>

Most of the recent research conducted by the HTC has been retrospective and records-based. There are two prospective trials being planned. One is to investigate healing rates and

successful wound closure in those with Wagner Grade II lower extremity diabetic wounds. Currently, Medicare and most third party insurers only cover diabetic lower extremity wounds for HBO when they are classified as Wagner Grade III or worse. Unfortunately, success rates for wound healing and limb salvage decline markedly as the Wagner score increases, and Wagner Grade III is defined as having exposed tendon and/or bone, with deep abscess and/or osteomyelitis which limits success to no better than 65%.<sup>11</sup> It is hoped that current reimbursement policies will change by demonstrating that substantially higher success rates could be attained by treating wounds at the Wagner Grade II level.

A second planned study is to explore the relationship of sympathomimetic decongestant use while diving and the risk for increased decompression stress. This project would attempt to verify the results of a recently concluded HTC records-based nested case control study which found that there may be increased risk for developing decompression sickness when using these drugs. It is hoped that these studies will be funded by grants. The HTC has also been very active in community service and education of the general public as well as the medical community via presentations at medical staff meetings, television and radio broadcasts, and through presentations to civic groups and organizations, as well as diving clubs and societies throughout the state.

Over the years, the HTC has operated with minimal staff essential to meet the established mission requirements. It has relied on the commitment and dedication of its staff to remain viable, relevant, and responsive. During the 25th Anniversary Celebration for the HTC, Dean Jerris Hedges referred to these efforts as a "labor of love." The changing times and circumstances since its founding have often presented challenges which have tested that dedication and ability of the staff to provide its essential services. Today the challenges which confront the HTC are largely driven by the nature of the economy as well as changing re-imbursement patterns of third party insurers which have led to a decline in revenues and threatens the long term viability of the HTC. Recently, the HTC joined the University Clinical, Education and Research Associates (UCERA) to improve and streamline its business practices and to ensure its sustainability into the future. It is believed this move will provide the HTC enhanced opportunities to pursue its unique but vital role.

The HTC has a history of service and contribution to the state. It has improved the health and well-being of hundreds of patients. It has broadened and deepened the knowledge and understanding of the field of undersea and hyperbaric medicine, and has added to improve diving safety. It remains an indispensable and critical asset for the State of Hawai'i, its people, and those who visit and may have need of the HTC's "specialized" services.

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## THEY CAN BE PENALIZED, BUT SELDOM REFORMED.

The Department of Justice announced that fiscal year 2011 yielded more than \$3 billion in settlements and judgments in civil cases involving fraud against the government. The bottom line included \$2.4 billion in recoveries for fraud committed against federal health care programs. The pharmaceutical industry was the source of \$2.2 billion; \$900 million came from 8 drug makers to resolve allegations of unlawful pricing to increase revenue. Senator Grassley (R-Iowa) authored amendments to the False Claims Act of 1986 that empowered whistleblowers to file suit on behalf of the United States. He stated, "Year after year, the federal False Claims Act proves to be the most powerful tool in rooting out fraud against the federal treasury." A few whistleblowers get rich. The drug people write a handful of checks, but no one goes to jail. The drug-buying patients get the BOHICA treatment (bend over here it comes again).

## GOOD NEWS: AUTO DEATHS DOWN. BAD NEWS: DRUG DEATHS UP.

Deaths caused by poisoning topped motor vehicle crashes in 2008 for the first time in at least three decades. The December report from the National Center for Health Statistics noted that deaths from auto accidents fell by almost half between 1980 and 2008 (22.9 down to 12.5 per 100,000). In the same time frame, the poisoning rate nearly tripled (4.8 up to 13.5 per 100,000). Sadly, poisonings involved prescription opioids in 40% of the deaths with the biggest increase in the past decade. Most commonly the drugs were morphine, hydrocodone (Vicodin) and oxycodone (Dazidox and others). Interesting to note that the death rate for all causes was 620 in the lowest state (Hawai'i) to 949 per 100,000 in the highest state (West Virginia). One more reason Lucky You Live Hawai'i.

## SOON THE WIRELESS WORLD WILL KNOW WHAT YOU HAD FOR BREAKFAST.

The Supreme Court of the United States unanimously ruled that police violated the Constitution when they attached a Global Positioning System (GPS) to a suspect's automobile. In a major test of privacy rights in the digital age, the Court held that the police action violated Amendment IV relating to unreasonable search and seizure. Four of the jurists pushed for a broader ruling, claiming that beyond the trespass violation, the suspect's movements were monitored for one month. This case is but the first of electronic surveillance with issues of email, cell phones, and on line documents still pending. Too bad! It seemed like such a great way to snoop into business where you should not.

## A NEW SUB-SPECIALTY: PSYCHIATRIC OPHTHALMOLOGY.

Previous studies have shown a link between strabismus and mental illness in adulthood. Constant exotropia is genetically associated with schizophrenia. Intermittent exotropia and convergence insufficiency have a 3-fold increased risk of mental illness. Now a study done at the Mayo Clinic Olmsted Group and reported in Ophthalmology documented the risk of mental illness in children born with congenital esotropia (CET). By following 127 patients from infancy to a mean age of 20.4 years, the team found that the development of mental illness was 2.6 times more probable compared with non-CET controls. Medical records were reviewed and the Diagnostic and Statistical Manual of Mental Disorders established criteria. A mental disorder was found in 22 (33%) of the males and 20 (30%) of the females. The men were most commonly diagnosed with major depression, attention deficit hyperactivity disorder, alcoholism, and drug use. The women suffered from major depression, adjustment disorder, and eating disorders. The cause of the association did not seem to be related to premature birth. No mention was made relative to surgical correction that might have altered the data.

## WE MUST ARREST THIS CRIMINAL — ALZHEIMERS DISEASE.

It's only rodents, of course, and the research is awaiting human trials, but the team at Case Western Reserve University in Cleveland quickly and dramatically improved brain function in mice bred to develop a form of Alzheimer's disease. Bexarotene, a cancer drug, cleared amyloid-beta cells in the protein of brains of stricken mice within days. Published in the journal Science, co-author Gary Landreth wrote what the drug does is to "help Mother Nature do what she normally does" in clearing amyloid fragments from the brain. First results were so surprising Landreth recalled, "It was unprecedented. I initially thought we had screwed up." Similar tests were done with over 100 mice fed with the drug. They quickly improved their cognitive, social and olfactory functions. Bexarotene is a long way from being an approved Alzheimer's drug or even being deemed ready for off-label use. Dr. Landreth plans to start a safety trial in a dozen patients in the next few weeks. Considering the pending tsunami of baby-boomers moving into retirement years, this work could be huge.

## COULD SHE FIT IN YOUR COUPE? BY HERSELF SHE'S A GROUP!

Reporting in the Archives of Surgery, a team of Swiss researchers gathered data to compare gastric bypass surgery with gastric banding to treat obese patients. Using a body mass index (BMI) of 30 or higher to define obesity, 442 patients were operated on between March 1998 and May 2005. At the start of the study the average BMI was 43. After a year, the average BMI in the bypass group fell below 30, while those receiving a gastric band had an average BMI of 34. Treatment was considered a failure if the BMI was 35 or higher at six years post surgery. Gastric banding had a failure rate of 48.3% compared with 12.3% for bypass. Initially gastric banding seemed safer than gastric bypass in the first three months, but what is important is how effective both procedures are. Moreover without treatment a great risk prevails

## THE G SPOT — A KEEN SKEIN DEFINED BY SKENE.

Managers of Prospect Park in Brooklyn, New York, wanted to move the statue of Abraham Lincoln to a more conspicuous location. The only possibility was to switch with the statue of Brooklynite Dr. Alexander Skene. But wait! Dr. Skene has his local advocates who defended his statue's location. He is remembered for his 1880 discovery and description of female peri-urethral glands that function like the male prostate gland. Moreover, Skene's glands are thought to be vital in understanding the female "G spot." And for this he gets a statue?

## ADDENDA

- Researchers at the University of Glasgow School of Medicine found that a serving of espresso coffee can deliver up to six times the estimate of caffeine for a single cup of coffee.
- 27% of Americans say broccoli is their favorite veggie.
- I didn't believe it, but it's true. You can now buy your sweetie vibrating panties for Valentine's Day or birthday.
- I visited my daughter to celebrate spring in Billings, Montana, last year. I missed it. I was in the bathroom.
- Bipartisan Democrat bumper sticker — I'll hug your elephant and you can kiss my ass.

## ALOHA AND KEEP THE FAITH *rts*

(Editorial comment is strictly that of the writer.)

# UPCOMING CME EVENTS

Interested in having your upcoming CME Conference listed? Please contact Brenda Wong at (808) 536-7702 x103 for information.

Date	Specialty	Sponsor	Location	Meeting Topic	Contact
<b>April 2012</b>					
4/1-4/6	GP, FM, GPM	University of California San Francisco School of Medicine	Wailea Beach Marriott, Maui	Primary Care Medicine: Update 2012	<a href="http://www.cme.ucsf.edu/cme">www.cme.ucsf.edu/cme</a>
4/14	GP, FM, GPM	University of Hawai'i, JABSOM, Area Health Education Program	Sheraton Waikiki, O'ahu	Hawai'i Physician Workforce Summit: Implementing Patient Centered Medical Home	<a href="https://adobeformscentral.com/?f=1ukFQNUGSHt1xX7O6Kq7Ug">https://adobeformscentral.com/?f=1ukFQNUGSHt1xX7O6Kq7Ug</a>
4/20	GYN, ON, GO	University of Hawai'i John A. Burns School of Medicine	Ala Moana Hotel, O'ahu	Gynecologic Oncology Conference 2012	Email: <a href="mailto:jlouis@ucera.org">jlouis@ucera.org</a>
4/20-4/21	ORS, OSM, OTR	Hawai'i Orthopaedic Association	Hawai'i Prince Hotel, Waikiki, O'ahu	27th Annual Combined Orthopaedic Spring Symposium	Email: <a href="mailto:cathy.iwai@hawaiiintel.net">cathy.iwai@hawaiiintel.net</a>
<b>May 2012</b>					
5/25	ADM, ADP	University of Hawai'i, JABSOM, Department of Psychiatry	Queen's Conference Center, O'ahu	Hawai'i Addictions Conference: Trends & Developments	Email: <a href="mailto:nmatsuda@dop.hawaii.edu">nmatsuda@dop.hawaii.edu</a>
<b>June 2012</b>					
6/13-6/16	OPH	UC Davis Health System	Hilton Waikoloa Village, Kohala, Hawai'i	35th Annual Ophthalmology Symposium, Big Topics on the Big Island: An Update of Comprehensive Ophthalmology	<a href="http://www.ucdmc.ucdavis.edu/cme">www.ucdmc.ucdavis.edu/cme</a>
<b>July 2012</b>					
7/1-7/6	OBG, REN	University of California San Francisco School of Medicine	Hapuna Beach Prince Hotel, Big Island, Hawai'i	Essentials of Women's Health: An Integrated Approach to Primary Care and Office Gynecology	<a href="http://www.cme.ucsf.edu/cme">www.cme.ucsf.edu/cme</a>
7/7-7/13	PD	Childrens Hospital Los Angeles Medical Group	Hyatt Regency Maui Resort & Spa	Pediatrics in the Islands... Clinical Pearls	<a href="http://www.childrenshospitalallamedicalgroup.org">www.childrenshospitalallamedicalgroup.org</a>
7/9-7/12	R	Postgraduate Institute for Medicine	Hyatt Regency Maui	Summer Imaging in Hawai'i	<a href="http://www.imaginginhawaii.com">www.imaginginhawaii.com</a>
7/17-7/20	EM	UC Davis Health System	Fairmont Kea Lani, Maui	Emergency Medicine Update: Hot Topics 2012	<a href="http://www.ucdmc.ucdavis.edu/cme/conferences">www.ucdmc.ucdavis.edu/cme/conferences</a>
7/29-8/2	ORS, OSM, OTR	Kaiser Permanente	Grand Hyatt Kauai, Kaua'i	20th Annual Update in Orthopaedic Surgery Conference	Email: <a href="mailto:kpos@sbcglobal.net">kpos@sbcglobal.net</a>
<b>August 2012</b>					
8/9-8/11	IM, FM	MCE Conferences	Disney Hawai'i Aulani Resort, O'ahu	Internal Medicine Update for Primary Care	<a href="http://www.mceconferences.com">www.mceconferences.com</a>
<b>September 2012</b>					
9/10-9/13	R	Postgraduate Institute for Medicine	Ritz-Carlton Kapalua, Maui	Imaging in Hawaii: Practical & Clinical Education	<a href="http://www.imaginginhawaii.com">www.imaginginhawaii.com</a>
<b>October 2012</b>					
10/22-10/26	GM, IM, FP	Continuing Education Company	Sheraton Maui Resort & Spa	2nd Annual Primary Care Fall CME Conference: Maui	<a href="http://www.cmemeeting.org">www.cmemeeting.org</a>
10/27-11/2	PD	Childrens Hospital Los Angeles Medical Group	Grand Hyatt Kaua'i Resort & Spa	Aloha Update: Pediatrics 2012	<a href="http://www.childrenshospitalmedicalgroup.org">www.childrenshospitalmedicalgroup.org</a>
10/3-10/6	CD	UC Davis Health System	Hilton Waikoloa Village, Kohala, Big Island, Hawai'i	32nd Annual Current Concepts in Primary Care Cardiology	<a href="http://www.ucdmc.ucdavis.edu/cme/conferences">www.ucdmc.ucdavis.edu/cme/conferences</a>



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