



HAWAI'I MEDICAL JOURNAL

January 2007, Volume 66, No. 1, ISSN: 0017-8594

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(USPS 237-640)

Published monthly by the
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Postmaster: Send address changes to the *Hawai'i Medical Journal*, 1360 South Beretania Street, Suite 200, Honolulu, Hawai'i 96814. Periodical postage paid at Honolulu, Hawai'i.

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FREE PARKING

Samoan Parental Ethnicity and Infant Birth-weight in Hawai'i

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Abstract

Objective: Comparative study of racial-ethnic (RE) gestational age (GA) mean birth-weight (MBW) differences for 1968-1994.

Study Design: Descriptive statistical analyses of 314,633 State of Hawai'i live birth certificates: birth-weights of 500-5000 grams, gestational ages 24-42 weeks, and recorded Caucasian, Chinese, Filipino, Hawaiian, Japanese, Samoan, and Other RE parentage. Multiple regression analyses of single infant birth records were performed to adjust birth-weight for selected covariates and assess the independent effects of maternal and paternal RE on MBW.

Results: Samoans consistently displayed significantly the largest MBW whether based on single or mixed RE parentage. After covariate adjustment MBW significantly related to Samoan maternal RE followed by Samoan paternal RE.

Conclusion: A consistent trajectory of larger MBWs across GA span of 24-42 weeks is associated with the Samoan group. Results support the importance of maternal role in determining birth-weight. Additional data for analysis of birth size and cord blood levels of insulin growth factor and research on genetic and epigenetic questions are warranted.

Introduction

Numerous studies describe differences in birth-weight (BW),¹⁻¹⁰ early childhood growth, and mortality across infant and mother racial-ethnic (RE) groups. These RE differences have been reported for the whole range of gestational ages (GA) along with increasing BW trends for specific RE populations in several countries.¹¹⁻¹⁴ With the exception of Morton,¹⁵ the association of parental RE with mean birth-weight (MBW) related to GA has not been extensively explored. Wang, Gayer, and Paige have reported differences in GA specific BW for three RE groups.¹⁶ Recently, McCowan and Steward¹⁷ developed ethnic specific BW centiles for New Zealand term (>37 weeks) infants. In two sets of these studies, one population group, in particular, stands out among all others: Samoan infants have the largest MBW in the state of Hawai'i¹⁵ as well as in New Zealand.¹⁷ The rich population variety in the state of Hawai'i offers opportunity for the further comparative study of RE differences with regard to trends in MBW.

This paper reports the results on the analysis of RE in relation to MBW with a focus on infants of Samoan mothers in Hawai'i.

Methods

State of Hawai'i birth record files for 1968-1994 showed 479,229 live births for this period of 27 years. Of these, 338,513 records with BWs between 500 and 5000 grams, GA for 24-42 weeks, and recorded ethnicity limited to Caucasian, Chinese, Filipino, Hawaiian, Japanese, and Samoan mothers and fathers, constituted this study data base. Apart from BW, information for the birth certificates was provided by the mothers. If ethnicity or educational level was not recorded in the birth certificate, then that pregnancy was not included. This reduced the number of records to 314,633. Gestational age was calculated from the date of last menstrual period as recorded on the birth certificate. This was the standard procedure during this period. These dates were retrieved from the patients' medical records as documented by their physicians. The date of the last menstrual period was reported anecdotally, but the accuracy of these dates is necessarily open to question.

From this study group further detailed analysis of 266,771 records of singleton births were selected for multiple linear regressions with adjustment for covariates. The covariate model included fourth order polynomials for year of birth and GA, a third order polynomial for mother's age, a second order polynomial for father's age, infant's gender, presence of congenital anomaly, the month of gestation in which prenatal care began, total number of prenatal care visits, the number of previous deliveries born alive still living, the number of previous deliveries born alive now dead, and legitimacy. In addition, month of birth was coded into 11 dummy variables with June as the reference. Education, measured as completed years of schooling, was grouped into five categories: <7 years, 7-11 years, 12 years, 13-16 years, and ≥ 17 years. Education was coded separately for fathers and mothers.

The number of singleton births with information on relevant covariates tabulated by parental RE show that infants of Caucasian and Hawaiian women comprise

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the largest percentages, 35% and 22%, respectively, while infants born to Samoan mothers are only about 2% of total births.

Results

Over four periods between 1968 and 1994 Samoan infants display the highest MBW among all the maternal ethnic groups at each time period, Figure 1. In Figure 2 are displayed MBW for GA of at least 29 weeks for the six maternal ethnicities; at lower GAs there were too few Samoan infants born at each age to have stable estimates of their means. The MBW of infants of Samoan mothers is the largest at each week of GA. Infants of Hawaiian mothers have the second largest MBW up to the 36th week of GA when the MBW of Caucasian infants overtakes the Hawaiians. For the displayed GA, infants of Chinese, Filipino and Japanese women have the lowest and fairly similar MBWs.

Table 1 shows MBW and maternal ethnicity at the 10th and 90th percentiles for mean gestational age groupings at 24-36 weeks and at 37-41 weeks. At each GA category infants of Samoan mothers have the largest MBW and the largest 10th and 90th percentile BW among all ethnicities. Three facts are evident in this table. The first reveals that not only are Samoan infants the heaviest for a GA at birth, but the value that delimits the lowest 10th percentile is shifted at least as much as the mean. This indicates that the difference in average MBW is not due to a few extremely heavy infants, but the entire distribution of MBW for Samoan infants has been shifted to the right. The second finding is that infants of Filipino mothers, while having the lowest average MBW for GAs of at least 37 weeks,

actually have relatively high MBW when born with a lower gestational age. The third finding is that for GA of at least 37 weeks, infants born to Hawaiian women do not have the second highest MBW; in fact, their MBW is approximately 200 grams lighter than the mean for infants born to Samoan women, despite being largely of Polynesian ancestry as are Samoans.

The effect of maternal ethnicity on MBW after adjustment for all covariates was very highly significant. The deviations from the MBW of infants born to Caucasian mothers are given in Table 2A. Except for Samoan infants, the MBW of every infant ethnicity was significantly lower than that of Caucasian infants. Adjusted for covariates plus maternal ethnicity, the MBW varied also by ethnicity of the fathers, Table 2B. The effect of having a Hawaiian father on mean birth-weight was about equal to the Hawaiian maternal effect. The other RE paternal effects were rather less than the maternal effect, this difference being particularly strong for Samoan fathers. Samoan mothers had infants averaging 191.5 grams more than infants of Caucasian mothers, but the paternal effect of Samoan fathers was only 67.1 grams.

There was an interaction of maternal age with mother's ethnicity. Birth-weight generally increased with maternal age. Compared to infants born to Caucasian mothers, average MBW of infants born to Hawaiian, Chinese, Japanese, and Filipino mothers increased more slowly with maternal age. The increase in MBW of Samoan infants was not significant. There also was a complicated interaction between maternal educational level and maternal ethnicity (p<0.01). Mean birth-weight increased gradually with maternal

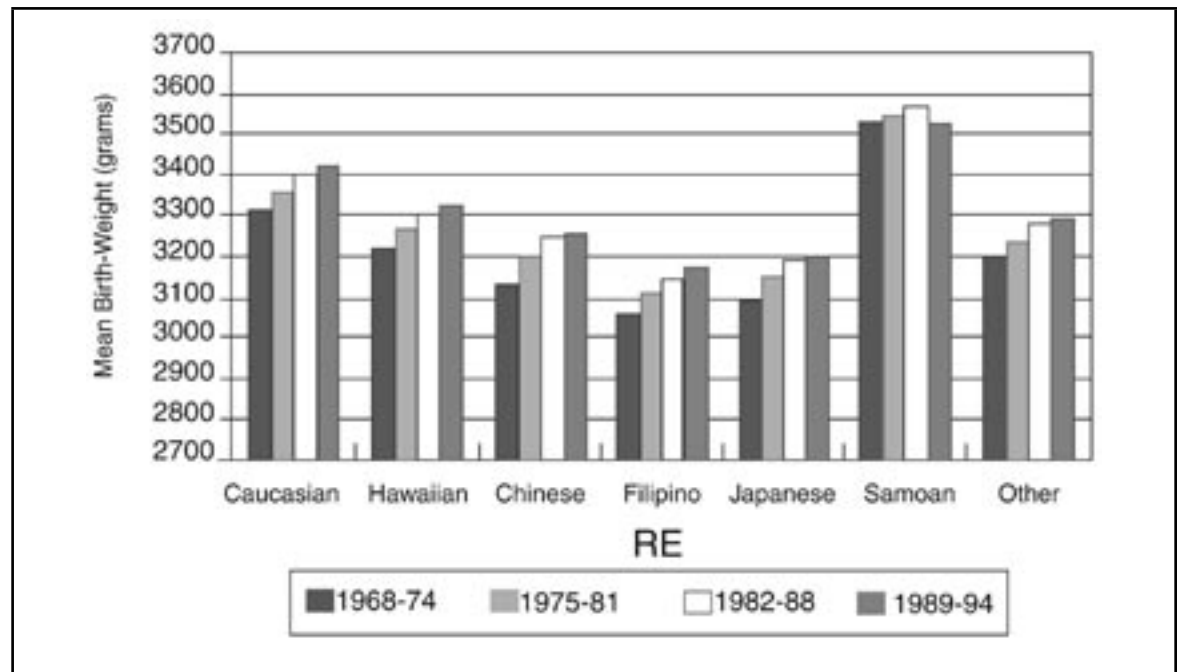


Figure 1.— Mean birth-weights of racial-ethnic (RE) groups over four periods: 1968-1994

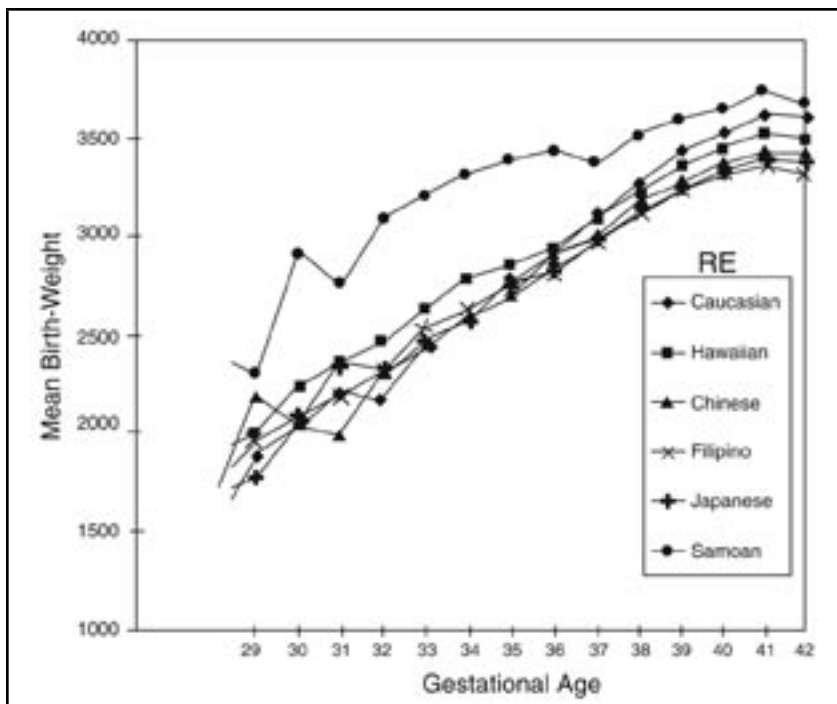


Figure 2.— Racial-ethnic (RE) mean birth-weights by gestational age

Table 1.— Maternal Racial Ethnic (MRE) Mean Birth Weights (MBW) with Standard Deviations (SD) for 10th, 50th, and 90th Percentiles (P) at Two Mean Gestational Age (MGA) Groupings.

MGA (Weeks)	MRE	N	MBW	SD	P10	P50	P90
24-36	Caucasian	8,615	2,547.07	756.407	1,481.00	2,600.00	3,462.00
	Hawaiian	7,434	2,690.54	728.143	1,729.00	2,750.00	3,570.00
	Chinese	1,085	2,558.17	710.922	1,620.00	2,635.55	3,430.00
	Filipino	7,138	2,603.20	661.279	1,730.00	2,656.00	3,388.00
	Japanese	4,504	2,522.17	688.167	1,615.00	2,576.60	3,345.00
	Samoan	878	3,201.90	750.590	2,235.00	3,274.00	4,054.00
37-41	Caucasian	100,366	3,422.19	482.722	2,334.80	3,416.00	4,026.00
	Hawaiian	61,916	3,336.51	478.882	2,750.00	3,325.00	3,941.00
	Chinese	12,773	3,261.34	425.109	2,749.95	3,260.00	3,799.00
	Filipino	55,436	3,185.56	444.640	2,637.00	3,175.00	3,750.00
	Japanese	48,312	3,209.76	427.111	2,689.00	3,203.00	3,755.00
	Samoan	6,176	3,586.35	488.461	3,000.00	3,572.00	4,210.00

education for Caucasian mothers, increased until 12 years of education and then leveled off for Hawaiian mothers, was highest for Chinese, Japanese, and Filipino mothers, who had 12 years of education and was lowest at 12 years of education for Samoan mothers.

Discussion

This study is the first United States based analysis to isolate infants of Samoan parents from Pacific Islanders. The MBW of Samoan infants is substantially higher than those of Caucasian, Asian, Filipino and Hawaiian groups. The infant MBW for Hawaiian mothers, who are of Polynesian ancestry, is not similar to the

MBW of infants born to Samoan mothers and actually is lower than for Caucasian infants. This finding is apparent, in spite of the fact that most of the non-Hawaiian ancestry of Hawaiian women is Caucasian.¹⁵ The highest significant effect of paternal ethnicity is noteworthy. The difference between the paternal effects of Hawaiians and Samoans is particularly intriguing. The fact that Samoans should be more similar genetically to Hawaiians than any of the other groups suggests that this difference between paternal and maternal effects is not genetic but a complex interaction of genetic and environmental factors.¹⁸⁻²⁰

Although there are always concerns on the accuracy of GA estimation the validity of the data on this issue warrants further detailed information and evaluation by sonic measurements when available. Unquestionably, the import of these data would be enhanced by information on the validity of GA estimation and the addition of other covariates influencing BW, for example, maternal height, pre-pregnancy body mass index, gestational weight gain, smoking, glucose tolerance, and gestational diabetes. These missing covariates do not necessarily detract from validity of these study results. Their value lies in insuring awareness of the impact of these covariates as determinants of fetal growth. The intent is to incorporate these issues in a newly formulated database for analysis over the ten year period 1994-2004.

In conclusion, the high BW of Samoan infants may primarily reflect the prevalence of obesity among Samoan women.^{18,19} Given the numerous reports relating birth-weight to subsequent risk of insulin resistance and chronic diseases,²¹ a compelling study is the comparison of hormone levels and growth trajectories among infants in Hawai'i. Among the intriguing hypotheses which warrant testing is whether the fetal insulin gene (INS) and the variable number of tandem repeats mini-satellites (VNTR) class III allele genotype are correlated with larger birth size and higher cord blood levels of insulin growth factor (IGF-11).²²

Acknowledgements

The assistance of the Department of Pediatrics, John A. Burns School of Medicine, University of Hawai'i at Manoa, the Chun Foundation for Medical Research in Pediatrics, and the Research and Statistics Office, Department of Health State of Hawai'i for birth certificate data are appreciated.

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Table 2A.— Deviations from Caucasian mothers' mean birth-weights (g) across racial-ethnic (RE) Groups.


RE Groups	Parameter Estimate*	Standard Error
Hawaiian	-51.97	2.40
Chinese	-134.59	4.42
Filipino	-176.29	2.46
Japanese	-179.74	2.66
Samoan	191.51	5.98

Table 2B.— Deviations from Caucasian fathers' mean birth-weights (g) across racial-ethnic (RE) Groups.

RE Groups	Parameter Estimate*	Standard Error
Hawaiian	-51.19	2.68
Chinese	-119.42	5.21
Filipino	-165.92	3.05
Japanese	-138.01	3.28
Samoan	67.13	7.06

*p<0.001


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Oriental Cholangiohepatitis from Outside of Asia

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Abstract

Oriental cholangiohepatitis, also known as recurrent cholangitis is exclusively endemic in Asian countries. Sporadic cases have been reported in the United States, however almost all cases have been seen in the Asian immigrants to the United States. We report a 31-year-old male from outside of Asia who developed oriental cholangiohepatitis.

Case

A 31 year old previously healthy male from Chuuk, one of the four island states that comprise the Federated States of Micronesia, presented with right upper quadrant pain with nausea and vomiting. He also reported fever and chills. He had been well until four months prior to presentation, when he was admitted to a hospital in Chuuk. At that time, he was found to have cholecystitis. He underwent cholecystectomy and common bile duct exploration with a finding of choledocholithiasis. AT-tube was also placed for biliary drainage, and then it was subsequently removed.

Five days after discharge from the hospital in Chuuk, he flew to O'ahu, Hawai'i to visit his family. Shortly after arrival in Hawai'i, he presented to the Emergency Department at the Queen's Medical Center for recurrent right upper quadrant pain as well as fever with chills. His temperature was 98 degrees Fahrenheit, blood pressure 117/77 mmHg, pulse 99 per minute and respirations 14 per minute. Oxygen saturation was 99% on room air. He did not appear acutely ill despite his abdominal pain. Mild scleral icterus was noted. Abdominal exam revealed tenderness in the right upper quadrant without guarding or palpable mass. The scar from his previous open cholecystectomy was well healed. The remainder of physical examination was unremarkable.

White blood cell count was 11,700 per mm³, AST 311 IU/L, ALT 518 IU/L, alkaline phosphatase 586 IU/L, total bilirubin 2.9 mg/dl, conjugated bilirubin 1.4 mg/dl and unconjugated bilirubin 1.5 mg/dl. CT scan of the abdomen revealed extensive choledocholithiasis with evidence of acute inflammation of biliary tract and pneumobilia.

As a result of these findings, a preliminary diagnosis of cholangitis was made, and piperacillin/tazobactam 3.375 grams IV every 6 hours was started. In addition to antimicrobial therapy, he underwent percutaneous transhepatic cholangiogram with the placement of a percutaneous biliary drain in the left hepatic duct.

Percutaneous transhepatic cholangiogram revealed multiple stones in both the right and left hepatic ducts, as well as in the common hepatic and common bile duct (Figure 1). Because of the persistent presence of extensive stones, a right internal-external biliary drain was also inserted. The patient then underwent percutaneous choledochoscopy and lithotripsy followed by balloon dilation of intrahepatic duct. Despite the performance of three percutaneous choledochoscopies with lithotripsy of hepatic duct stones, multiple stones in the hepatic duct were not removed completely.

On hospital day 3, his abdominal pain and fever subsided. Bile cultures grew, *E.Coli*, susceptible to piperacillin/tazobactam. He was discharged with plans for more lithotripsy as an outpatient.

He had been well without symptoms after discharge; however two days prior to a scheduled lithotripsy, he returned to the emergency department with fever, chills, and right upper abdominal and back pain. White blood cell count showed 11,500 per mm³, AST 95 IU/L, ALT 120 IU/L, alkaline phosphatase 305 IU/L, total bilirubin 1.5 mg/dl, and conjugated bilirubin 0.3 mg/dl. Ceftriaxone 1g IV q24h and Tobramycin 380 mg IV were administered.

Over the next forty eight hours, his symptoms resolved so he underwent repeat percutaneous choledochoscopy. There was a marked reduction in the amount of stones in the right intrahepatic duct with some residual stones in the common bile hepatic duct. The patient still had extensive stones in the left hepatic duct including a 2 cm stone. Repeated balloon dilation of the ampulla followed by electrohydraulic lithotripsy was performed. The right hepatic duct was cleared of all the remaining stones, and most of stones were extracted from left intrahepatic duct. Ova and parasites were not found in his stool. Biliary fluid culture grew an ESBL (Extended Spectrum Beta Lactamase)-producing *E.coli* and *Stenotrophomonas maltophilia*. Antimicrobial therapy was changed to imipenem/cilastatin 500 mg IV q6h and trimethoprim/sulfamethoxazole 10 ml IV q12h.

After repeated balloon dilation of the ampulla followed by electrohydraulic lithotripsy, patient developed acute respiratory failure, which required intubation, mechanical ventilation, and transfer to the ICU. Within 72 hours after transferred to the ICU, patient's condition improved and he was successfully



Figure 1.— Multiple contrast defects of intrahepatic duct with stricture by percutaneous transhepatic cholangiogram.



Figure 2.— Transhepatic cholangiogram after the removal of multiple intrahepatic biliary stone.

extubated. He continued to improve clinically following transfer out of the ICU; however the biliary drainage fluid culture still remained positive for ESBL-producing *E. coli* despite appropriate antimicrobial therapy. On hospital day 12, he again developed abdominal pain with nausea and vomiting. Repeat choledochoscopy was performed which revealed the presence of extensive stones in the right hepatic duct where it was cleared out previously and 0.5 cm sized stone in the proximal part of the left hepatic duct. He underwent repeat lithotripsy.

One week after the last choledochoscopy, the patient was taken for a third round of choledochoscopy. Unfortunately, he was again noted to have recurrent hepatolithiasis with sludge in the right hepatic duct and common intrahepatic duct; the stones were extracted by lithotripsy. There were no residual stones remaining in the left hepatic duct.

He repeatedly underwent repeat choledochoscopy on the hospital day 30, which showed some residual stone in the right hepatic duct, but this was successfully treated with lithotripsy. Antimicrobial therapy was continued for a total 30 days.

A final choledochoscopy revealed some residual stones, but because of the reduction in the amount of stones and a significant improvement in the patient's clinical status, the patient was discharged in good condition on hospital day 32. The patient underwent 4 numbers of choledochoscopies and eventually had the majority of stones removed. Some residual debris was left behind but did not create any significant biliary obstruction (Figure 2).

Discussion

Oriental cholangiohepatitis is virtually exclusively seen in a limited geographic area, especially in countries in Southeast Asia, Taiwan and Japan.^{1,2} However, this disease has become more prevalent in the United States, with an influx of immigrants from endemic areas.^{2,3} It is characterized by recurrent cholangitis, multiple stone formation in the intrahepatic duct and stricture of the biliary tree.

The pathogenesis of cholangiohepatitis is stone formation and bile stasis, while the etiology of the stone formation and stasis themselves are poorly understood. Because of these unique characteristics, many theories have been proposed such as intrahepatic stone formation

secondary to parasitic infection, bacterial infection or nutritional status.

Oriental cholangiohepatitis is most prevalent in rural, lower socioeconomic groups. It has been suggested that liver flukes, including *Clonorchis sinensis* or *Ascaris lumbricoides* may contribute to the development of oriental cholangiohepatitis.^{2,4} Huang et al reported a relationship between hepatolithiasis and helminthic infestation. They concluded helminthiasis is a possible risk factor for hepatolithiasis, although it is unlikely to increase the incidence of complication, including bile duct stricture secondary biliary cirrhosis and cholangiocarcinoma.⁵ Despite the suggestion of parasitic infestation as an etiology for this disease, oriental cholangiohepatitis is common in countries without these parasites. For example, *Clonorchis* or *Ascaris* infection is no longer a prevalent infection in Japan where hepatolithiasis still persists.⁶ Current consensus of the association with parasitic infection is inconclusive, and thus the association between parasitic infection and oriental cholangiohepatitis is probably incidental rather than causative.²

The diagnosis of oriental cholangiohepatitis is usually established by clinical presentation, as well as radiographic or ultrasonographic findings.⁷⁻⁹ Several authorities conclude that ultrasonography might be superior for detecting intrahepatic stone and intrahepatic dilation and stricture.^{10,11} MRCP (Magnetic Resonance Cholangiopancreatography) is also helpful to visualize intrahepatic lesions.¹²

Oriental cholangiohepatitis usually presents with fever, jaundice, and abdominal pain. In addition to optimal choice of antimicrobial agents, clearing intrahepatic stones is critical in order to prevent recurrence.

The standard surgical approach for patients with intrahepatic stones includes cholecystectomy, resection of the extrahepatic biliary tree to include any strictures or choledochal cyst followed by choledochoscopy and extraction of any intrahepatic stones. Partial hepatic resection may be required in patients with segmental atrophy or cirrhosis. Because of recurrent stones formation, approximately 50% of patients with intrahepatic stones require further procedures such as balloon dilation of biliary tract to clear the recurrent intrahepatic ducts of stones or to manage persistent strictures.

In addition to standard surgical approach, various methods are

debated to remove intrahepatic stones including therapeutic ERCP (Endoscopic Retrograde Cholangiopancreatography), percutaneous choledochoscopy, choledochenterostomy, electrohydraulic lithotripsy, and their combination.^{8, 15-17} However, there is no clear evidence suggesting any method is superior to the other.

Our case is classical for oriental cholangiohepatitis. The patient presented with recurrent cholangitis, and was found to have multiple contrast defects of intrahepatic duct with stricture by percutaneous transhepatic cholangiogram. Although no parasites were identified in the stool and the bile, a diagnosis was made from the clinical manifestations and radiographic findings.

There have been several cases of oriental cholangiohepatitis published in the United States; however, patients in these articles have been exclusively Asian immigrants. Only two articles of cholangiohepatitis in western patients were published from Spain and Australia.^{13,14}

In our case, the patient is from Chuuk, one of the four island states that comprise the Federated States of Micronesia. The Federated States of Micronesia are freely associated with the United States, a political relationship which grew out of the UN-mandated United States Trusteeship.

Chuuk and much of the remainder of Micronesia was under League of Nations mandate to Japan following the close of World War I, during which Japan had taken control of the islands from Germany. Extensive Japanese settlement occurred during this period, with Japanese nationals outnumbering Chuukese by 10,000 to 40,000. The relationship with Japan lasted until the end of World War II. Despite the end of the Trusteeship in 1990, citizens of the CNMI (Commonwealth Northern Marianas Islands), FSM (Federated States of Micronesia) and Republic of the Marshall Islands continue to travel to Hawai'i to seek medical care under the terms of the Compacts of Free Association. The impetus behind much of the medical travel is a lack of medical resources in Micronesia, as well as unrestricted immigration for Micronesians into and out of the United States.

In summary, we report a case of oriental cholangiohepatitis from outside of Asia. Because it possibly occurs in populations outside of Asian countries, Oriental cholangiohepatitis should be considered in patients with recurrent cholangitis regardless of their country of origin.

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Metabolic abnormalities associated with atypical antipsychotics: a case report and alert

Teruo Yamauchi MD and Alan Tice MD



Teruo Yamauchi MD



Alan Tice MD

Abstract

We report a case of a 29-year-old man with schizoaffective disorder in which diabetes mellitus and hypertriglyceridemia developed with quetiapine (Seroquel®). We reviewed the literature on the relationship between antipsychotic therapy and development of metabolic disorders and found serious concerns. This case demonstrates the importance of a careful monitoring of glucose and other metabolic parameters in patients receiving atypical antipsychotics.

Introduction

Atypical antipsychotics are commonly used for psychoses due to their reduced extrapyramidal side effects and more favorable psychiatric outcomes compared with typical antipsychotics. Quetiapine (Seroquel®) is one of the atypical antipsychotics used for the treatment of schizophrenia and other psychoses. It binds to a wide variety of receptors including dopaminergic (D1 and D2) and serotonergic (5-HT1A and 5-HT2) receptors. Hyperglycemia and diabetes mellitus have been reported as uncommon side effects by manufacturers.¹ However, there have been reports in the literature of the possible association of diabetes mellitus with the use of many atypical antipsychotics.²⁻¹⁷ The following is a case report of possible quetiapine-induced onset of diabetes mellitus.

Case report

The patient was a 29-year-old Hawaiian man with a history of schizoaffective disorder. He had no prior history of hyperglycemia nor a family history for diabetes mellitus. He had, however, gained 50 pounds with the last year. Several months before his admission, he was started on quetiapine for a schizoaffective disorder. His compliance with medication was poor and he shared the medication with his brother who also had a psychosis. One month before admission, he began to take quetiapine daily before bedtime because of insomnia. One week prior to admission, he presented to the emergency room with complaints of polydipsia and polyuria. His blood glucose was greater than 600 mg/dL. He was treated by his primary care physician but admitted to the hospital a week later with persistent hyperglycemia with a glucose of 563 mg/dL despite

insulin therapy. He did not have ketoacidosis but was noted to have hypertriglyceridemia (TG > 1000 mg/dL) with total cholesterol 290 mg/dL and HDL 14 mg/dL. Amylase and lipase were 64 IU/L and 24 IU/L, respectively. He was given intravenous fluid and a base of insulin 70/30 twice daily plus a sliding scale for insulin therapy. He required dose escalation of 70/30 insulin as high as 50-60 units twice daily to achieve control of glucose. After discontinuation of quetiapine, his insulin requirements steadily decreased. He was discharged to be followed by his primary care physician and on gemfibrozil for hypertriglyceridemia.

Discussion

We considered many factors as possible etiologies for diabetes in this case. These included obesity, pancreatitis, hemochromatosis, hyperthyroidism, and Cushing's syndrome. Weight gain may have contributed but would not explain the full presentation. Quetiapine is the most likely precipitating factor for this patient's hyperglycemia because of the temporal correlation and known adverse effects of antipsychotics. Quetiapine is one of the atypical antipsychotics that are dopamine and serotonin receptor blockers while typical or traditional antipsychotics such as phenothiazines (such as chlorpromazine) and butyrophenones (such as haloperidol) are dopamine receptor blockers. Atypical antipsychotics have been increasingly used for psychoses because of reduced extrapyramidal side effects and favorable cognitive and psychiatric outcomes.

Metabolic derangements associated with antipsychotics have been reported previously. Reports of diabetes associated with antipsychotic mediations date back to the 1950s when chlorpromazine was found to induce diabetes in mice.^{18,19} More recently, there are also reports of diabetes with the atypical antipsychotics including clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole.²⁻¹⁷ The postulated underlying mechanisms for hyperglycemia may include 1) decreased sensitivity to insulin that is independent of atypical antipsychotics, 2) increased insulin resistance related to these medications, 3) the effects of these medications on serotonin receptors, and 4) insulin resistance or abnormal production due to

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Antipsychotics	Hyperglycemia	Hypertriglyceridemia	Hypercholesterolemia	Weight gain ¹ (w: weeks)
clozapine	0.1-1.0%	ND ²	ND ²	4%
risperidone (Risperdal®)	0.1-1.0%	<0.1%	ND ²	18% (6 to 8w)
olanzapine (Zyprexa®)	0.1-1.0%	0.1-1.0%	0.1-1.0%	short-term (6w): 5.6% long-term (median 238 days): 56%
quetiapine (Seroquel®)	0.1-1.0%	17%	11%	23% (3 to 6w)
ziprasidone (Geodon®)	0.1-1.0%	<0.1%	0.1-1.0%	10% (4 to 6w)
aripiprazole (Abilify®)	0.1-1.0%	0.1-1.0%	0.1-1.0%	short-term (4 or 6w): 8% long-term (26w): 5.1-6.8% long-term (52w): 8-30%

1: weight gain: >= 7% of baseline body weight, 2: ND: not documented
Reference: Physician's Desk Reference 59th Edition, Thomson PDR, Montvale, N.J., 2005

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine (Zyprexa®)	+++	+	+
Risperidone (Risperdal®)	++	D	D
Quetiapine (Seroquel®)	++	D	D
Aripiprazole (Abilify®)*	+/-	-	-
Ziprasidone (Geodon®)*	+/-	-	-

+ = increase effect; - = no effect; D = discrepant results. *Newer drugs with limited long-term data
Adapted from 2004 American Diabetic association and American Psychiatric Association Consensus statement. *Diabetes Care*. 2004; 27(2):596-601.

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status.
Adapted from 2004 American Diabetic Association and American Psychiatric Association Consensus statement. *Diabetes Care*. 2004;27(2):596-601.

weight gain.²⁰ Obesity, ethnicity, family history of diabetes mellitus, and weight gain during the course of treatment have all been identified as risk factors for the development of hyperglycemia in patients with schizophrenia.

Manufacturers report metabolic abnormalities as uncommon side effects in the Physician's Desk Reference (Table 1).¹ An incidence of hyperglycemia is reported for all the atypical antipsychotics but only up to 1%. However, retrospective data analyses demonstrate that there is considerable evidence that atypical antipsychotic medication can cause hyperglycemia.²¹ Weight gain is also consistently noted with these medications, especially with long-term use. A recent review by the American Diabetic Association with the American Psychiatric Association is displayed in Table 2 with less quantitative results.²² The potential consequences in terms of cardiovascular diseases, liver disease, chronic kidney disease, metabolic problems, and unnecessary additional medications to control them must be considered.

Clinicians should be aware of possible metabolic complications and periodic monitoring of laboratory studies and attention to the signs and symptoms of hyperglycemia are important in the care of patients receiving atypical antipsychotics. A consensus statement by the American Psychiatry Association and the American Diabetes Association issued in 2004 addressed this problem. Table 3 displays their recommendations.²²

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Primary cutaneous cryptococcosis in Hawai'i

Christopher W.M. Soon BS and Allan K. Izumi MD



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Abstract

A 72-year-old man developed a primary cutaneous cryptococcal skin infection on the right forearm, which was responsive to oral fluconazole 400 mg per day. After 16 weeks of treatment, the skin lesion completely resolved without any residual scarring.

Introduction

Cryptococcosis is an opportunistic infection caused by *C neoformans*, an encapsulated, usually spherical yeast. In the era of AIDS, organ transplants, and corticosteroid use, it has become a leading cause of morbidity and mortality in these patients.¹ Disseminated meningoencephalitis is the most common symptomatic manifestation.² Infection is rare in non-immunocompromised hosts, with incidences ranging from 0.2 to 0.9 per 100,000 in non-HIV affected individuals, but has a high prevalence in immunocompromised HIV-infected individuals, ranging from 2.9 to 13.3%.³

Case Report

A 72-year-old Caucasian man with a 25 year history of asthma requiring prednisone 5 to 10 mg per day developed a painful nodule on the right forearm, which progressed to an eczematous dermatitis. The eczematous component improved on aluminum acetate compresses and topical steroids. Two months later, there was a persistent asymptomatic indurated plaque associated with epidermal atrophy and purpura (Figure 1). A KOH preparation was negative. Biopsy revealed a granulomatous dermal infiltrate extending to the subcutaneous fat with numerous oval clear cells which were PAS positive (Figure 2). No hyphae were present. Fungal culture subsequently revealed *Cryptococcus neoformans*.

The patient did not recall previous trauma to the forearm, but did note that pigeons fly about his yard. He had no weight loss, headache, fever, or other signs of systemic involvement. Laboratory data included a CBC with white blood count $14.0 \times 10^9/L$ (4.8 to 10.8×10^9) with 87% neutrophils, 7% lymphocytes, 3% monocytes, and 3% eosinophils. Hemoglobin was 12.6 g/dL (14.0 to 18.0), hematocrit was 39.0% (42.0 to 52.0), and the platelet count was $257 \times 10^9/L$ (140 to 440×10^9). Serum protein electrophoresis and the T cell subset panel were normal. Serum cryptococcal

antigen was positive, with a titer of 1:512. Chest x-ray was normal. An indium-111 white blood cell scan and a technetium-99m bone marrow scan revealed a small focus of abnormal WBC localization in the soft tissue of the patient's right arm, with no other significant abnormality.

He was given oral fluconazole 400 mg per day for 16 weeks with subsequent resolution of the infection without significant residual scarring.

Discussion

C neoformans is ubiquitous in the soil, but the excreta of birds (especially pigeon droppings) are well known reservoirs.⁴ *C neoformans* has also been recovered from decaying wood,⁵ fruits, vegetables, and dust.^{6,7} Four serotypes have been identified. Serotype A (*C. neoformans* variety *grubii*) has a worldwide distribution. Serotype D (*C. neoformans* variety *neoformans*) is found mostly in Europe and can be isolated in avian excreta. Serotypes B and C (*C. neoformans* variety *gattii*) are limited in tropical and subtropical areas, and have been associated with eucalyptus trees.⁸ To our knowledge, there are no published epidemiological studies comparing the incidence of cryptococcal infections in Hawai'i versus the mainland United States. However, there was a study published in 1969 documenting the isolation of *C. neoformans* from various avian droppings collected from soil samples throughout Oahu.⁹ *C. neoformans* was isolated mostly from pigeon droppings especially in Waipahu, rarely from chicken droppings, and absent from mynah bird or seabird droppings.

Although there are no immunological markers documenting that the patient was immunocompromised, we believed that the chronic use of low dose prednisone in the range of 5 to 10 mg over 25 years was sufficient to cause skin atrophy, fragility, and purpura. Patients receiving 1 to 10 mg of prednisone per day have been reported to have an increased risk for infection.¹⁰ The initial clinical picture of eczematoid dermatitis could have either been a primary cryptococcal cellulitis or a bed for accidental inoculation and subsequent primary cutaneous cryptococcal infection. Although it is difficult to distinguish primary cutaneous cryptococcosis (PCC) from secondary cutaneous cryptococcosis, we feel that our patient had PCC because there was no clinical or

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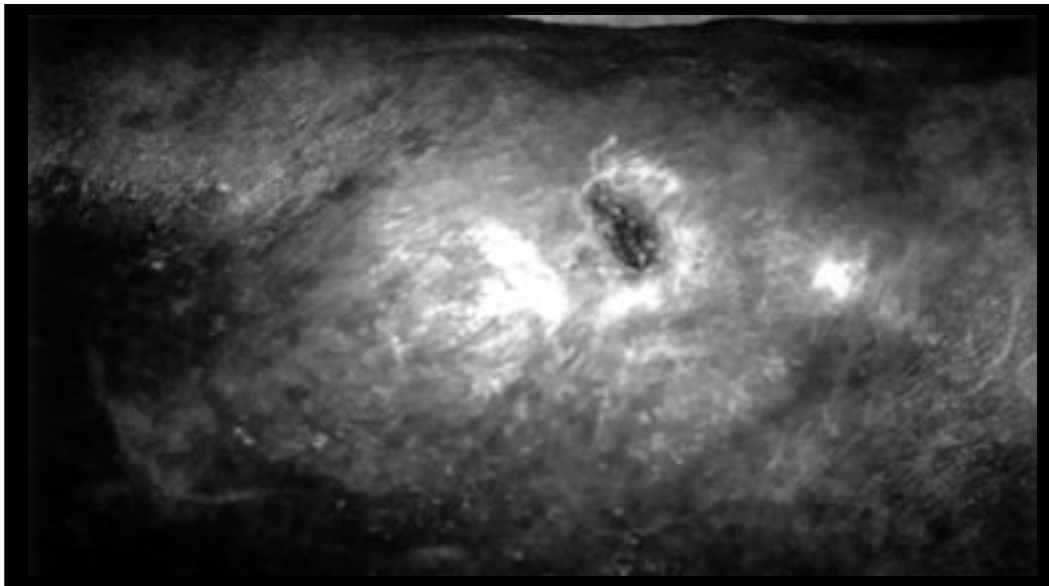


Figure 1.— Inflammatory indurated plaque on the right arm (biopsy site at center).

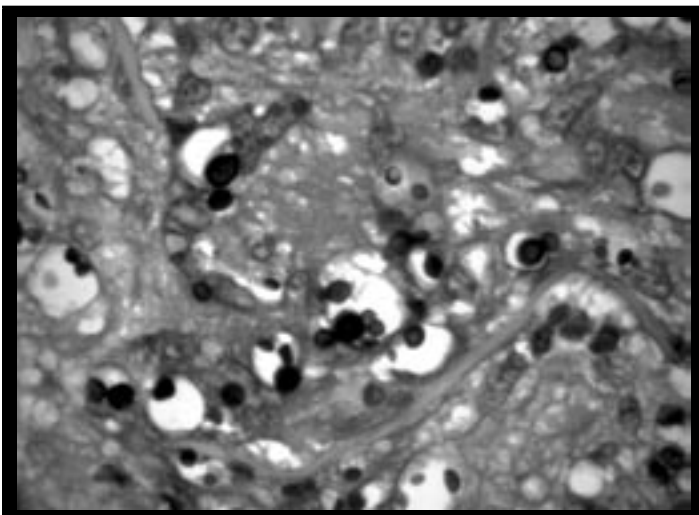


Figure 2.— Multinucleate giant cells containing intracytoplasmic PAS-positive cryptococcal forms (PAS, 1000X original magnification).

laboratory evidence of primary cryptococcal infection of the lungs or central nervous system.

PCC is rare and results from direct contact or trauma to the skin, usually in exposed areas. It presents as a solitary or localized lesion, including whitlow, nodule, plaque, ulceration, and cellulitis. There are no systemic signs, and the patients are usually healthy. In one study, 50% of patients with PCC had no underlying disease predisposing to cryptococcosis.⁸ Serum cryptococcal antigen is usually negative, but secondary antigenemia may occur if other criteria are fulfilled.¹¹

In secondary cutaneous cryptococcosis resulting from dissemination, umbilicated papules are the most common presentation, especially on the face, although a variety of lesions can be seen, including cellulitis, pyoderma gangrenosum-like lesions, and a combination of polymorphic lesions. These patients are usually

ill from their underlying disease. In a study, 90% of patients with secondary cutaneous cryptococcosis had an underlying disease predisposing them to cryptococcosis, and 58% were infected with HIV.⁸

The treatment and prognosis in secondary cryptococcal skin infections is variable, whereas the treatment and prognosis of PCC is good and includes local surgical removal and/or systemic use of antifungals including fluconazole, ketoconazole, itraconazole, or amphotericin B.¹²

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Grants Supporting Health Programs for Hawai'i and Pacific Islands at the John A. Burns School of Medicine

**Gregg Takayama, Director, Public Relations,
John A. Burns School of Medicine**

Recent federal grant awards continue to give the John A. Burns School of Medicine a prominent role in improving future health conditions for residents of Hawai'i and the Pacific Islands. Included among the major, funded projects in 2006 are the following:

Translational Award

JABSOM is among 52 institutions selected to participate in an initiative by the National Institutes of Health aimed at speed in translating medical discoveries into improved medical care. The awarded titled, Clinical and Translational Science Award (CTSA), is a competitive award granted by the National Institutes of Health (NIH). Included among other recipients are Harvard, Stanford, and Brown universities.

This is a planning grant of \$190,350. These funds will enable joint initiatives between units at the University of Hawai'i at Manoa, as well as community and industry partners. Included in the UH Manoa consortium are JABSOM, Cancer Research Center of Hawai'i, School of Nursing and Dental Hygiene, College of Tropical Agriculture and Human Resources, Pacific Biosciences Research Center, the Department of Electrical Engineering, Department of Anthropology, Department of Psychology, and Department of Information and Computer Sciences.

"The CTSA program encourages our nation's research institutions to foster productive collaboration among experts in different fields, lower barriers between units, and find ways to better service the medical needs of the community," says UH Manoa Vice Chancellor Gary Ostrander, Interim Dean of JABSOM and principal investigator of this research initiative.

David Easa, MD, Director of Clinical Research at JABSOM added: "We will work together in an interdisciplinary fashion to evaluate and develop new treatments and insights into disease prevention that can be more efficiently delivered to patients."

Pacific Island health

JABSOM received a federal grant of \$400,000 to continue an interdisciplinary project aimed at improving the training of health care workers in the Pacific Islands, utilizing distance-education technologies where feasible. This U.S. Health Resources Service Administration (HRSA) award is in direct response to the Institute of Medicine Report that detailed great disparities in availability of continuing education for all of the health workforce in the U.S. Associated Pacific Island entities.

A major UH Manoa partner participating in the four-year, \$1.6 million project is PEACESAT which enables the UH Medical School to coordinate long-distance health training via satellite and other distance-education technologies. The federally funded project covers

the Territories of American Samoa, and Guam, Commonwealth of Northern Marianas, the Federated States Micronesia, Republic of Palau, and the Republic of the Marshall Islands.

Detailed needs assessments were performed in the first year of the project. An analysis of the findings showed a general lack of infrastructure in support of continuing education opportunities for nurses, allied health, and physicians, especially those in the Freely Associated States (Yap, Chuuk, Pohnpei, Kosrae). In addition, the findings confirmed that Pacific Islanders suffer disproportionately high rates of diabetes, cancer, cardiovascular disease, and oral health problems, and have life expectancies as much as 12 years lower than U.S. life expectancies.

Principal Investigator Neal Palafox MD, MPH, and Project Director Lee Buenconsejo-Lum MD of the Department of Family Medicine and Community Health reported, "We've worked collaboratively with other national and international partners who currently provide educational opportunities for the health workforce in the region and have leveraged resources to help the jurisdictions move toward developing sustainable continuing education programs, including developing local and regional expertise. There remain great disparities in the amount of money spent toward educating the health workforce in the FAS or territories, compared to the United States."

Youth anti-violence

JABSOM's Department of Psychiatry has been awarded a federal grant to serve as a national coordinating center for scientific studies aimed at reducing youth violence. Funding for the first year is \$194,600.

This four-year grant will enable UH Manoa to coordinate youth violence prevention efforts with 10 prestigious institutions in the United States. The granting agency is the Centers for Disease Control and Prevention (CDC).

"Youth violence spans across all cultures with many cultural differences playing a role. This valuable research will contribute to the nation's knowledge of what works to help reduce and prevent youth-related violence," says JABSOM faculty member Dr. Gregory Mark, the Principal Investigator.

Dr. Earl Hishinuma, Principal Investigator and Director of the Asian/Pacific Islander Youth Violence Prevention Center, added, "The Coordinating Center will be able to integrate the participating centers into a focused effort to address youth violence prevention. The Asian/Pacific Islander Youth Violence Prevention Center is honored to be awarded the Coordinating Center."

The UH Youth Violence Prevention Research and Mobilization Center began in 2000 at several Honolulu high schools and communities. Currently, the Center includes several community-based

Continued on p. 21



The Non-invasive Diagnosis of Lymph-node Status Based on Gene Expression Profiles of Primary Breast Cancer Tumors

Gordon S. Okimoto PhD, Director, Informatics Shared Resources,
Cancer Research Center of Hawai'i

Introduction

The ability to predict the clinical outcome of breast cancer, including lymph-node metastasis or recurrence, will profoundly affect the clinical decisions made to manage disease progress. For example, the presence of metastatic breast cancer in axillary lymph nodes is probably the most significant factor in overall survival.¹ Although the determination of lymph node status is relatively routine, the surgical procedure is highly invasive, and selectivity in identifying nodes for examination introduces biases that suggest some reported negatives may indeed be truly positive.² The ability to accurately predict axillary lymph node status on the basis of a gene expression profile of the primary tumor may obviate the need for axillary lymph node dissection and the significant morbidity associated with this procedure.³

The focus of this article is on the non-invasive diagnosis of lymph-node status based on gene expression profiling of the primary tumor. A closely related goal is the identification of the genes and pathways that are highly correlated with changes in lymph-node status using DNA microarrays. Previous attempts to correlate characteristics of primary tumors such as S-phase fraction, tumor grade, ploidy, hormone receptor status and ERBB2 over-expression with lymph-node status have been unsuccessful. Our studies show that gene expression profiling appears to have the resolution necessary to characterize lymph-node status using as few as 35 genes. In addition, the genes, pathways and phenotypic models that result from a genome-wide analysis of gene expression in breast cancer tumors provide hypotheses for highly focused molecular studies with the potential to identify new targets that may contribute to improved treatment and care, and a deeper understanding of the causal mechanisms underlying metastasis and tumor growth.

Microarrays and Microarray Experiments

DNA microarrays (or chips) profile the steady-state messenger-RNA (mRNA) levels of thousands of genes simultaneously in a single biological sample. A microarray experiment consists of multiple microarrays each profiling a distinct biological sample. The goal of a typical microarray experiment is to characterize changes in a clinical phenotype, such as lymph-node status, in terms of a small number of genes that are differentially expressed between the two conditions. This is accomplished by statistically comparing the global gene expression patterns of two groups of samples with known lymph-node status. Given that the human genome is composed of tens of thousands of genes, and that microarray data is inherently noisy, this comparison poses a difficult analytical problem. We have developed a method of analyzing these data to achieve high accuracy in determining whether a primary tumor has metastasized to the lymph-nodes based on the gene expression profile of the tumor.

The Data

The data presented in this article were downloaded from a public repository of microarray data made available by Duke University Institute for Genome Sciences and Policy. The original data consisted of primary tumor biopsies obtained from the Koo Foundation Sun Yat-Sen Cancer Center in Taipei, Taiwan and Duke University. Tumors were either positive for both the estrogen and progesterone receptors or negative for both receptors. Each tumor was diagnosed as invasive ductal carcinoma and was between 1.5 and 5 cm in maximal dimension. In each case, a diagnostic axillary lymph node dissection was performed and lymph-node status was determined. Total RNA was extracted from tumor tissue, processed and hybridized to Affymetrix U95-AV-5 GeneChip microarrays using standard protocols established by the vendor. Each microarray profiled the steady-state mRNA levels of 12,625 genes simultaneously in a single tumor sample. The final data consisted of 37 microarrays of which 19 were associated with lymph-node negative (negative) samples and 18 were associated lymph-node positive (positive) samples.

Statistical Analysis

The 37 GeneChips were arranged as the columns of a data matrix A , that had 12,625 rows and 37 columns. The columns of A were ordered so the chips associated with negative samples occupied columns 1 thru 19, while the positive chips occupied columns 20 thru 37. The columns of A were normalized to facilitate comparison between chips, and logarithmically transformed to equalize random variation over expression intensity. A novel signal detection algorithm called MANINI was then applied to the rows of A to identify genes that were significantly altered in expression in the positive sample class. Such genes are called significant genes.

Figure 1 shows the results of a MANINI analysis of the data matrix A in the form of a Ratio/Intensity scatter plot. Every point of the R/I plot represents the average fold change (vertical axis) versus average expression (horizontal axis) of a single gene in the log-log space. Genes that are significantly up-regulated on positive samples are highlighted with open circles, while genes that are significantly down-regulated on the positive samples are highlighted with open triangles. MANINI found that 448 genes were significantly up-regulated, while 391 genes were found to be significantly down-regulated for a total of 839 genes significantly altered in expression in the positive breast cancer tumors.

The list of significant genes was further reduced to a list of significant pathways (or gene networks) where each pathway is a collection of interacting genes that accomplishes a specific biological function. The Ingenuity Pathway Analysis (IPA) tool was used to identify the significant pathways contained in the MANINI gene list. IPA is a proprietary knowledgebase containing what is cur-

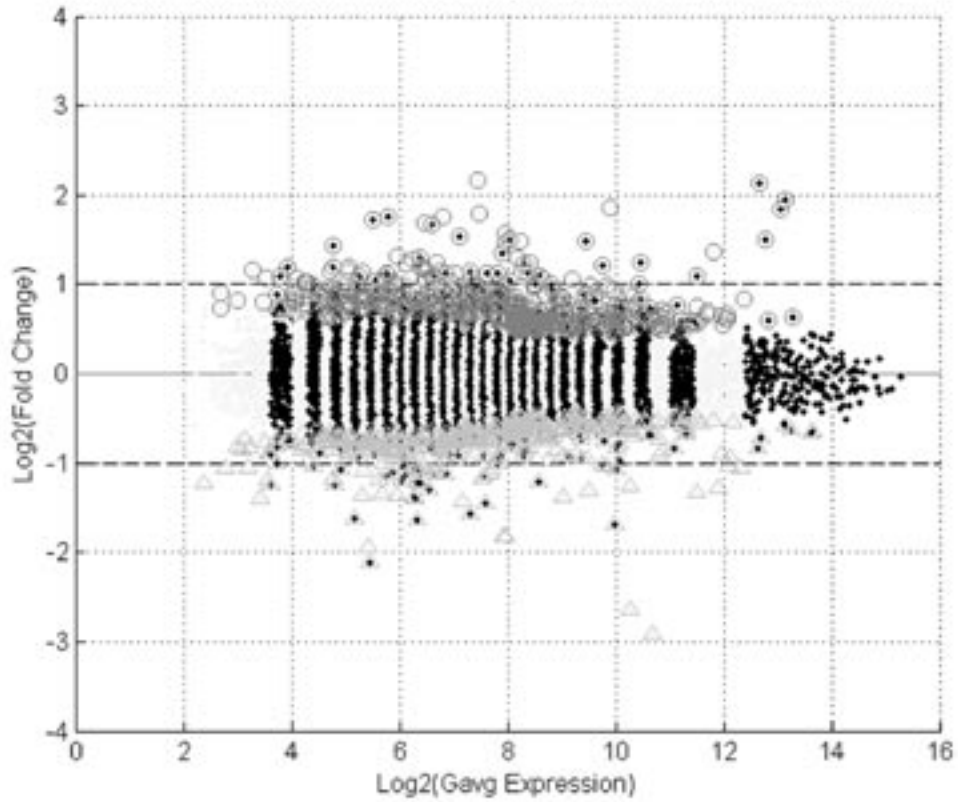


Figure 1.— Ratio/Intensity plot of the Huang breast cancer data set with up-regulated genes highlighted with open circles and down-regulated genes highlighted with open triangle. The other points represent noise in the data. A total of 839 genes were called significantly altered in expression on the positive samples using the MANINI detection algorithm.

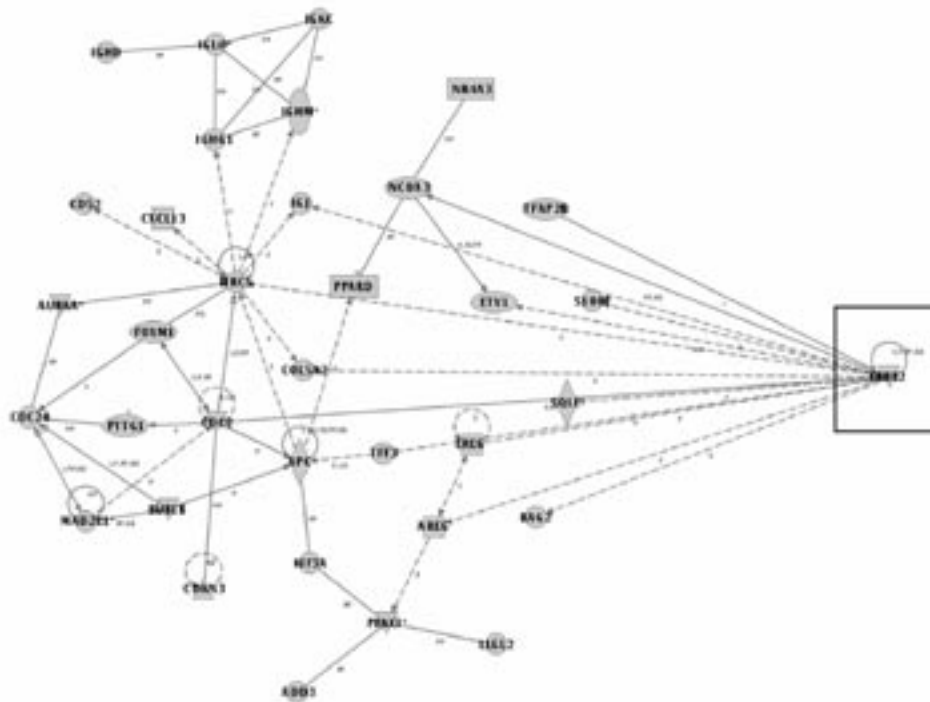


Figure 2.— Network diagram of the most significant pathway discovered in the 448 up-regulated genes identified by the MANINI algorithm. Each node represents a gene and each edge connecting two genes represents an interaction between them. The ERBB2 gene which is the target for the cancer drug Herceptin is highlighted in the square box.

Name	Description	Drugs
ADD3	adducin 3 (gamma)	
APC	adenomatosis polyposis coli	
AREG	amphiregulin (schwannoma-derived growth factor)	
AURKA	aurora kinase A	
BAG2	BCL2-associated athanogene 2	
BIRC5	baculoviral IAP repeat-containing 5 (survivin)	
BUB1B	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	
CD52	CD52 molecule	alemtuzumab
CDC2	cell division cycle 2, G1 to S and G2 to M	flavopiridol
CDC20	CDC20 cell division cycle 20 homolog (S. cerevisiae)	
CDKN3	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)	
COL5A2	collagen, type V, alpha 2	collagenase
CXCL13	chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)	
ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	trastuzumab, BMS-599626, lapatinib
EREG	epiregulin	
ETV1	ets variant gene 1	
FOXM1	forkhead box M1	
IGHD	immunoglobulin heavy constant delta	
IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	
IGHM	immunoglobulin heavy constant mu	
IGJ	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	
IGKC	immunoglobulin kappa constant	
IGL@	immunoglobulin lambda locus	
KIF3A	kinesin family member 3A	
LLGL2	lethal giant larvae homolog 2 (Drosophila)	
MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	
NCOA3	nuclear receptor coactivator 3	
NR4A3	nuclear receptor subfamily 4, group A, member 3	
PPARD	peroxisome proliferative activated receptor, delta	
PRKCI	protein kinase C, iota	
PTTG1	pituitary tumor-transforming 1	
S100P	S100 calcium binding protein P	
SQLE	squalene epoxidase	
TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	
TFF3	trefoil factor 3 (intestinal)	

Figure 3.— A list of significant genes contained in IPA network #2. This network was used to pathway compress the Huang breast cancer data set to select the most informative genes related to lymph-node status. Note the presence of ERBB2 and the drugs that use this gene as a target.

rently known about gene function and gene-gene interactions. We considered only the 35 genes in IPA network #2 which had a p-value of 10^{-52} and inferred functions of *cellular growth and proliferation* and *immune response*. The process of focusing only on genes in a significant IPA network is known as *pathway compression*. An interaction diagram of IPA network #2 is shown in Figure 2 and a list of the genes contained in the network is shown in Figure 3.

The expression profiles of the 35 genes in IPA network #2 were then wavelet transformed to enhance signal-to-noise ratio and compressed down to 10 features for each sample using singular value decomposition (SVD). SVD compression in the wavelet domain is a novel method of identifying features in microarray data that are useful for pattern recognition applications in cancer diagnosis and prognosis. A neural network classifier was trained to predict the lymph-node status of a sample based on its 10-dimensional feature vector.

The ability of the NN classifier to diagnose positive lymph-node involvement was objectively evaluated using leave-one-out cross validation (LOOCV) analysis. Here, a sample is “left-out” of the data set and the remaining data are processed as described above resulting in a trained neural network classifier that is then used to classify the left-out sample. The neural network output is compared with the known lymph-node status of the sample and the result is duly noted. The process is repeated for every sample in the data set and the percentage of left-out samples that were correctly diagnosed represents the correct classification rate (CCR) for the system. LOOCV analysis was repeated 50 times to determine system robustness and the median CCR over the 50 trials was computed.

LOOCV analysis of the neural network described above resulted in a median CCR of 95%, that is, the lymph-node status of 35 out of 37 samples were correctly diagnosed based on the gene expression patterns in the primary tumor. Only 35 genes were used to achieve this high CCR value. This result compares favorably with the result of the original Huang study that achieved a CCR of 90% using 200 genes. Interestingly, the network of 35 genes used to train the neural network classifier contained the ERBB2 (Her2/neu) gene, which is the target for the cancer drug Herceptin. Moreover, this gene was absent from the 200 significant genes identified in the Huang study. This result suggests that pathways modulated by drugs like Herceptin may be involved in the progression of breast cancer from low to high risk status.

The results summarized above suggest that global patterns of gene expression in primary breast cancer tumors contain sufficient information to diagnose lymph-node status provided proper information processing techniques are employed. Pathway compression, wavelet signal processing and SVD combine to achieve a significant reduction in the number of genes that must be considered in the modeling process without significant loss of relevant information.

For more information on the Cancer Research Center of Hawai‘i, please visit its website at www.crch.org.

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Issues in Medical Malpractice VII

S.Y. Tan MD, JD

**Professor of Medicine and Adjunct Professor of Law
University of Hawai'i**

QUESTION: Mary visited her favorite sister Cecilia in the hospital where she had recently undergone brain surgery. During the visit and in full view of Mary, Cecilia developed *status epilepticus* after a nurse gave her Dilaudid instead of Dilantin. Mary was petrified by the incident and developed insomnia, nightmares and depression.

- A. Cecilia can sue the nurse for medical malpractice.
- B. Mary can sue for the negligent infliction of emotional distress.
- C. The hospital may be liable even if the nurse was an independent contractor from an outside agency.
- D. The doctor will be sued because his illegible handwriting caused the wrong medication to be administered.
- E. The suit will likely fail because seizures are a common post-op event after brain surgery, and the wrongly administered drug may not have been the offending agent.

ANSWER: All correct. In this case, several parties will be named as co-defendants, including the nurse, the doctor, and the hospital. Mary also has a cause of action against the co-defendants as her emotional injuries occurred in close proximity to her sister's injury. If the nurse is an independent contractor, presumably with separate insurance coverage, the hospital may attempt to get out of the lawsuit, but plaintiff may argue successfully that the nurse was an "ostensible agent", or that the hospital failed to properly credential, supervise, etc. If the doctor's illegible order is shown to be the reason for the error, then the doctor will clearly be at risk. However, the nurse still has an independent duty to clarify the order especially if it's for an unusual drug or an unusual dose. Finally, as in all malpractice claims, the plaintiff must prove, by preponderance of expert evidence, the element of causation, i.e., but for the wrong drug being administered, seizures would not have developed. The facts here suggest that proving causation may be difficult for the plaintiff(s), as seizures may well have resulted from brain surgery itself rather than medication error.

Causation

After the plaintiff has established that the doctor owes a duty and experts have persuaded the court that there has been a breach of the standard of care, the plaintiff will still need to prove causation to have an actionable negligence case. There are two types of causation, factual cause and proximate cause.

Factual Cause: Factual cause is also known by terms like cause-in-fact, actual cause, or physical cause. It is established by the use of the 'but-for' test. The typical law-school definition goes something like this:

*"the defendant's conduct is a factual cause of plaintiff's injuries if plaintiff's harm would not have occurred but for defendant's conduct," or "the defendant's conduct is a factual cause of plaintiff's injuries if plaintiff's harm would not have occurred without defendant's conduct."*¹

It is the plaintiff who must prove with a preponderance of evidence that the negligent act caused the injury. A good example is *Roskin v Rosow*.² An internist prescribed Questran for a patient with hypercholesterolemia. Constipation resulted, and the patient was taken off medication after 7 months. However, she was again placed on Questran the following year, and the dosage was in fact increased from four to six packets per day. Colestid was subsequently substituted for Questran, and at about the same time, she received Codeine for pain. A month later, the patient experienced severe abdominal pain, and a barium enema revealed a perforated sigmoid colon. She underwent emergency surgery; the colon was found to be distended, with impacted feces 'the size of tennis balls.' Plaintiff sued internist, alleging negligence in prescribing Questran and Colestid after she had complained of constipation, and negligence in prescribing Codeine which aggravated the constipation, caused fecal impaction, colon distension, and perforation.

The defendant contended that plaintiff reported only mild constipation, and that the bowel was perforated during the barium enema, not from the use of medications. Plaintiff demanded \$500,000, which was then reduced to \$300,000; defendant offered \$100,000. There being no settlement, the case went to trial and the jury found for the defendant. **Reason:** plaintiff did not satisfy causation element.

Proximate Cause: Factual cause is just one of two prongs needed to establish the causation element in the tort of negligence. The plaintiff also has to prove proximate cause, which speaks to the court's limit of how far it will go to impose liability upon the defendant for his or her actions. In the words of a Court of Appeals of Arizona:

*"A plaintiff proves proximate cause, also referred to as legal cause, by demonstrating a natural and continuous sequence of events stemming from the defendant's act or omission, unbroken by any efficient intervening cause, that produces an injury, in whole or in part, and without which the injury would not have occurred."*³

The concept of proximate causation has confused generations of students, but the basic idea is simply to show a reasonable causal connection between negligence and harm, i.e., that substandard care caused the injury in a foreseeable manner. It will be discussed in greater detail in a subsequent article.

Pre-Existing Conditions: Some patients may harbor preexisting conditions that predispose them to greater injury, however trivial

the inciting negligent act. The law will compensate the plaintiff for an aggravation of a pre-existing condition if such aggravation was caused by defendant's negligence. Take as an example a diabetic with peripheral neuropathy and poor circulation. A negligently treated foot ulcer may cause the patient to end up with an amputation, whereas such a serious outcome will be less likely in a non-diabetic patient. In this example, the negligent doctor will be responsible for all injuries, including the amputation, though not for the pre-existing condition itself, i.e., the diabetic state.

The 'Eggshell skull rule' is the most extreme example of 'taking your victim as you find him.' The doctrine originated in the 1901 English case of *Dulieu v. White*, where the plaintiff with a thin skull died from a minor accident whereas a normal person would have suffered only a bump on the head.⁴ The defendant was found liable for the patient's death.

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

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4. *Dulieu v. White*, 2 K.B. 669 (1901).

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Medical School Hotline, from p. 16

groups on methods of curbing youth violence by bridging cutting-edge science with practice.

Dr. Ileana Arias, CDC Injury Center Director commented, "We are pleased that the University of Hawai'i will serve as the Coordinating Center to help us face the critical challenge of bringing science to practice so we can protect our youth from violence."

The National Academic Centers of Excellence on Youth Violence Prevention (ACEs) include: Columbia University; Harvard University; Johns Hopkins University; University of California, Berkeley; University of California, Riverside; University of Illinois; Virginia Commonwealth University; Children's Hospital of Philadelphia; and Meharry Medical College, Tennessee.

Eco-health

A \$3.1 million federal grant to JABSOM will fund an innovative 5-year project that enables doctoral students to explore connections

between disruptions in Hawai'i's ecosystems with rises in infectious diseases. The interdisciplinary program spans six departments of UH Manoa and three scientific institutes.

The new two-year program has begun with five doctoral fellowships. The aim is to build a cadre of scientists trained in working across academic disciplines and spanning different social cultures.

The program is directed by Dr. Bruce Wilcox, Chairman of the Division of Ecology and Health in the JABSOM's Department of Tropical Medicine, Medical Microbiology and Pharmacology.

In the next 5 years, it is anticipated that an expanded roster of JABSOM faculty and students will continue to compete nationally for awards and grants that will contribute to the foundation of scientific knowledge.

Fight the Flu!

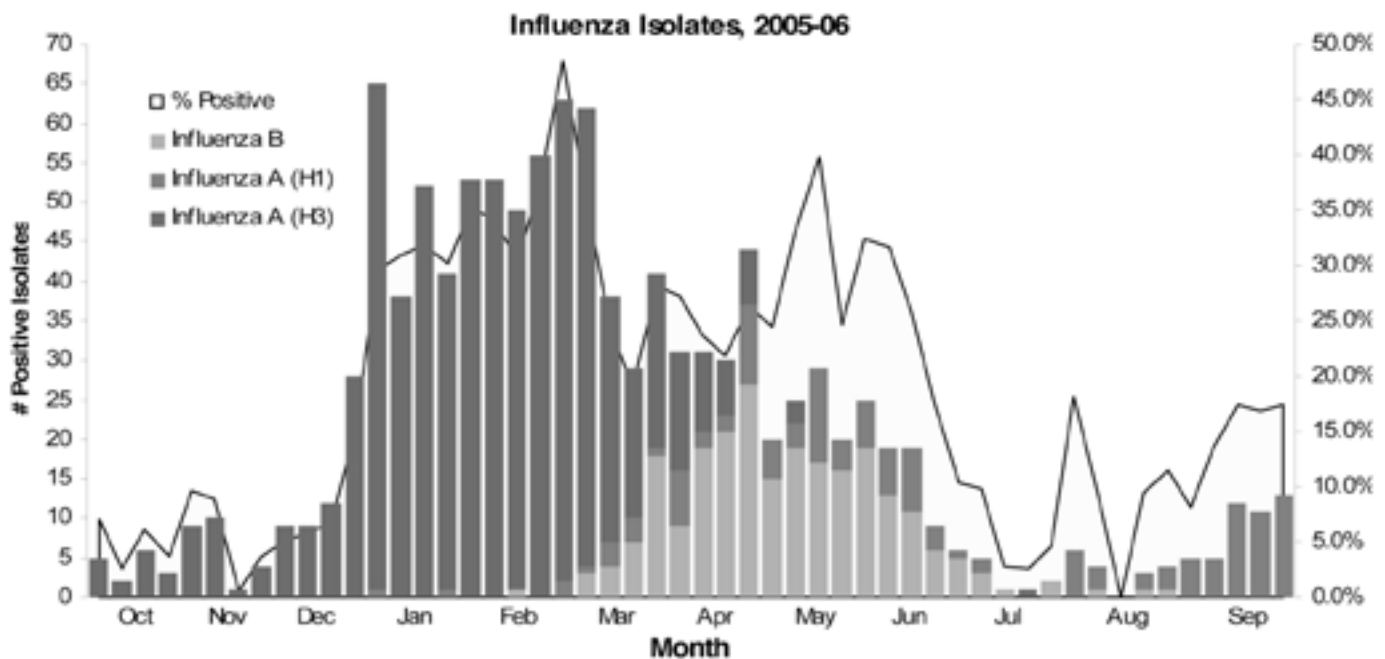
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Date	Specialty	Sponsor	Location	Meeting Topic	Contact
February 2007					
2/2-2/3	P	Mayo Clinic College of Continuing Medical Education	Sheraton Kauai Resort, Poipu Beach, Kaua'i	Psychiatric Pharmacogenomics	Tel: (480) 301-4580 Web: www.mayo.edu/cme
2/3-2/4	OPH	Hawai'i Ophthalmological Society	Halekulani Hotel, Honolulu	23rd Annual Hawai'i Ophthalmological Spring Update	Tel: (808) 521-3535 Email: mwseminar@yahoo.com
2/4-2/9	GS, VS, TS	Mayo Clinic College of Continuing Medical Education	Wailea Beach Marriott Resort & Spa, Wailea, Maui	Mayo Clinic Interactive Surgery Symposium	Tel: (480) 301-4580 Web: www.mayo.edu/cme
2/10-2/16	PD	University Childrens Medical Group	The Westin Maui	Pediatric Potpourri State of the Art 2006	Tel: (800) 354-3263 Web: www.ucmg.org/cme.html
2/10-2/16	NPM	Keck School of Medicine of USC	The Westin Maui	Perinatal Medicine 2007	Tel: (800) 872-1119
2/12-2/16	IM, FM	Mayo Clinic College of Continuing Medical Education	Sheraton Keauhou Resort, Kona	Selected Topics in Internal Medicine	Tel: (480) 301-4580 Web: www.mayo.edu/cme
2/14-2/18	OBG	University of Hawai'i Department of OB/GYN and Women's Health	Hyatt Regency Waikiki Resort & Spa, Honolulu	Evidence-based OB/GYN: Practical Application of New Advances	Tel: (808) 203-6528 Email: ckawahar@hawaii.edu
2/14-2/18	OBG	University of Hawai'i Department of OB/GYN and Women's Health	Hyatt Regency Waikiki Resort & Spa, Honolulu	Contemporary OB/GYN Ultrasound: Recent Advances and Clinical Practice	Tel: (808) 203-6528 Email: ckawahar@hawaii.edu
2/17-2/24	OTO	Otolaryngology Research Foundation	Hilton Hawaiian Village, Honolulu 2/17-2/20 Hyatt Regency Hotel, Kaanapali Beach, Maui 2/21-2/24	Otolaryngology Updates	Tel: (916) 923-0820
2/18	R	Mayo Clinic College of Continuing Medical Education	Hapuna Beach Prince Hotel, Kohala Coast	Advanced Radiology Life Support Course	Tel: (480) 301-4580 Web: www.mayo.edu/cme
2/18-2/23	R	University of California, San Francisco	Fairmont Orchid Hawai'i, Kamuela	Body Imaging in Paradise	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
2/18-2/23	Multi	University of California, San Francisco	Grand Hyatt, Kaua'i	Infectious Disease in Clinical Practice	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
2/22-2/27	GE	Keck School of Medicine of USC	Mauna Kea Beach Resort, Hawai'i	Medical and Surgical Aspects of Esophageal and Foregut Disorders: Pathophysiology and Treatment	Tel: (800) 872-1119
2/24	Multi	The Queen's Medical Center	Koolau Golf Club	Connecting the Dots: The Queen's Medical Center Conference on Quality and Patient Safety	Tel: (808) 537-7009 Email: cme@queens.org

Continues on next page

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March 2007					
3/3	Multi	Hawai'i Chapter of the American College of Physicians	Hawai'i Prince Hotel	Annual Scientific Meeting	Tel: (808) 586-7478 Email: sharonch@hawaii.edu
3/3-3/10	IM, FM	Keck School of Medicine of USC	Mauna Kea Beach Resort, Hawai'i	Diagnostic Skills in Internal Medicine	Tel: (800) 872-1119
3/5-3/9	Multi	St. Francis International Center for Healthcare Ethics	Hawai'i Medical Center -- East	Becoming an Ethics Consultant	Tel: (808) 547-6050 Web: www.bioethicshawaii.org
3/14-3/17	Multi	Symposia Medicus	Kaua'i Marriott Resort, Lihue, Kaua'i	14th Annual Spring Conference on Women's Health	Tel: (800) 327-3161 Web: www.symposiamedicus.org
3/19-3/23	END	Mayo Clinic College of Continuing Medical Education	Hapuna Beach Prince Hotel, Kohala Coast	An Intensive Review of Endocrinology for the Clinician	Tel: (480) 301-4580 Web: www.mayo.edu/cme/
3/28-3/31	Multi	Symposia Medicus	Kaua'i Marriott Resort, Lihue, Kaua'i	6th Annual Spring Conference on Hot Topics in Primary Care Medicine	Tel: (800) 327-3161 Web: www.symposiamedicus.org
April 2007					
4/3-4/5	P	State of Hawai'i Adult Mental Health Division	Hawai'i Convention Center, Honolulu	Work Works! Supported Employment: The 4th Annual Best Practices Conference	Tel: (808) 586-4686
4/08-4/13	PCP	University of California, San Francisco	Wailea Beach Marriott Resort & Spa, Wailea, Maui	Primary Care Medicine: Update 2007	Tel: (415) 476-5808 Web: www.cme.ucsf.edu
4/11-4/14	PD	Symposia Medicus	Kaua'i Marriott Resort, Lihue, Kaua'i	11th Annual Spring Conference on Pediatric Emergencies	Tel: (800) 327-3161 Web: www.symposiamedicus.org
4/15-4/20	DR	University of California, San Francisco	The Fairmont Orchid, Kamuela, Hawai'i	Diagnostic Imaging on Kona	Tel: (415) 476-5808 Web: www.cme.ucsf.edu

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THE WEATHERVANE

RUSSELL T. STODD MD, CONTRIBUTING EDITOR



Russell T. Stodd MD

❖ A LUXURY IS SOMETHING YOU DON'T NEED BUT HAVE TO HAVE.

How do you sell an expensive intra-ocular lens implant to the Medicare cataract population? Thanks to direct to consumer advertising (DTC) multiple avenues are available. *ReZoom* the multi-focal implant made by Advanced Medical Optics, Inc. (AMO) decided on a well known senior golfer, Gary Player. The screen shows him putting out with a birdie on the first hole, and attributing his skill largely to his sharp vision with the implanted lens. Now he is the paid spokesman for AMO, and the campaign includes a package of television,

radio and print ads. *ReStor*, the competing lens from Alcon Laboratories Inc., features a handsome white-haired grandmother type with a young lad beside her on safari. She is wearing no glasses of course, as she reads from her guidebook and spots gazelles, elephants, and other game. The marketers have learned from Lasik that it is best to get the manufacturer out of the loop, and have local ophthalmologists tie their personal footage to the mini-drama. So far, sales are lagging. The hard part is explaining to elderly patients why they need to buy a \$4000 implant instead of a pair of drug store reading glasses.

❖ SIGN ON THE EMERGENCY DEPARTMENT DOOR "CLOSED TODAY. BACK TOMORROW MAYBE."

In our Aloha state, new doctors are not coming, some established docs are leaving, older physicians are retiring, and if we didn't have the John A. Burns School of Medicine, access to care would be folklore. It doesn't have to be this way. In 2003 Texas passed tort reform by way of public referendum and the malpractice climate has changed. Doctors are more likely to accept patients with high-risk problems and physician recruiting is now much easier. According to Medical Economics the Texas state medical board expects to receive 4,500 new physician license applications this year, an increase of 40% over 2005. The board executive director attributes tort reform as the "only viable hypothesis" to explain the huge increase.

❖ TO MINIMIZE LOSS DUE TO EARTHQUAKES TRY NOT TO OWN THINGS.

The October 15, 2006, earthquake that shook the Hawaiian Islands should serve as a wake-up call for all of us, because defects in preparedness showed up in multiple areas. Certainly the most difficult to comprehend was the near total loss of electric power which lasted all day on Oahu. Hawaiian Electric failed to offer a satisfactory explanation. More significantly, why was there no Civil Defense emergency radio broadcast? KSSK, a Honolulu commercial outlet, fired up emergency generators to provide the only information obtainable. The Hawai'i Health Systems Corporation management got egg on its face because the structural defects which resulted in damage at Kona Hospital had been previously reported by Civil Defense. That report was either not read or was ignored. The absence of injury to patients and staff was just good luck, because if the Richter reading had been slightly higher Kona Community Hospital might have been a pile of rubble and a state government scandal could have ensued.

❖ HURRAH! IT'S A GIANT STEP...SIDEWAYS.

Hawai'i has mandated that at least 85% of gasoline sold after April 2006 contain 10% ethanol. The green people cheer because it is cleaner, less pollution, a great step ahead! But is it really? What it also means is that your miles per gallon will drop by 20 to 25%. Consumer Reports tested a Chevrolet Tahoe and found that highway mpg dropped from 21 to 15, and city mileage went from 9 to 7. Who really benefits from this great leap forward? The highly subsidized and tax supported corn and grain growers of middle America, principally Archer Daniels Midland (recently fined \$100 million for anti-trust violations) are delighted, and so are the oil companies since fewer miles per gallon means increased fuel sales. Our generous Hawai'i legislature passed a law which gives investors \$2 tax

credit for every \$1 spent on building an ethanol plant, plus five additional tax breaks. The Alaska Science Forum as far back as 1980 found that the cost of producing and harvesting the biomass (irrigation, fertilizer, etc), plus plant construction, and the energy required for production totals out to a negative. In summary, gasohol may be cleaner, but it looks like a loser. And guess who has to pay the bill for reduced gas mileage, agribusiness subsidies, and tax credits?

❖ IN AN AIRCRAFT THERE IS NO SUCH THING AS A LITTLE PROBLEM.

As passengers were exiting an Air France flight from Manchester, England, a large and hairy spider fell from the overhead baggage compartment, delaying the Airbus's return to Paris by five hours. The spider was never found. A Swissair Airbus bound for Vienna was grounded for two days as personnel searched and eventually trapped a rat. In Zurich, Switzerland, a flight to Moscow was delayed for almost two hours because an eight inch snake was spotted. The serpent had escaped from the pocket of a young man who had slipped it by U.S. Security agents. It was a harmless snake, but still represented a major concern for both passengers and crew. Many such events happen every year as aircraft are held up by mice, rats, snakes, spiders and in one case by a pit bull terrier. It had escaped from the cargo hold and chewed up parts of the plane and gnawed on electrical cables as big around as a garden hose. To date, there has been no recorded crash caused by stowaway critters, and certainly the delays don't amount to much dollar loss compared with the cost of jet fuel, still it is a genuine issue for passenger angst and air transport carriers.

❖ ALWAYS SAY NO TO DRUGS. THAT WILL DRIVE THE PRICES DOWN.

To the dismay of the American pharmaceutical industry, U.S. Customs and Border Protection officials have been told to stop seizing prescription drugs imported through the mail from Canada. For over a year, the practice was depriving tens of thousands of American seniors of their medicine and protecting the outrageous prices of American drug companies. Although it is illegal under U.S. law, Canadian and U.S. Customs had turned a blind eye to these puny orders, but the Pharmaceutical Research and Manufacturers of America had argued about the "dangers of unsafe imported drugs." What a crock! Everyone (even the Dubya administration spokesperson) admits that the bulk of profits for drug manufacturers comes right out of the pockets of America's seniors.

❖ SO THAT'S WHAT GRANNY WAS DOING BACK THERE IN THE STACKS.

In Levy County, Florida, public libraries have seen a 97% reduction in their volunteer help. New county regulations require that all employees and volunteers be tested for drugs. They are told to "pee in the cup" within earshot of a supervisor. Because most of the volunteers are retired people who help stock and arrange the bookshelves, they have refused to oblige and given up this generous task. "Why are we spending tax money to test 75-year-old grandmothers for marijuana?" said one silver-haired lady.

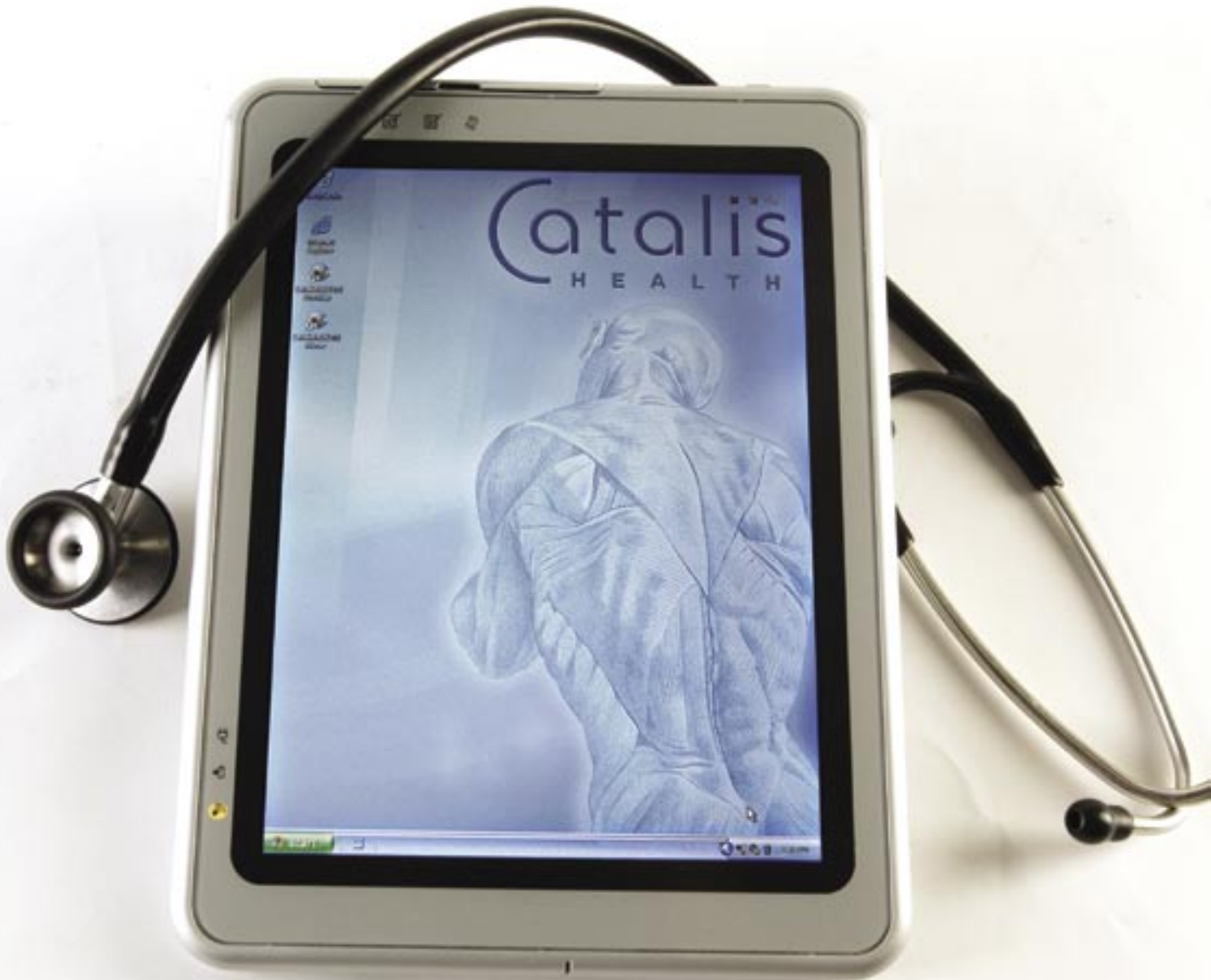
ADDENDA

- ❖ According to government statistics flu kills 3% of patients age 65 to 84, and 8% of those 85 and beyond.
- ❖ If you are average, your lacrimal glands put out about four quarts of tears per year.
- ❖ Coca-Cola can be used to clean your toilet bowl.
- ❖ If a human sperm were the size of a salmon it could swim at 500 miles per hour.
- ❖ Wilma Flintstone's maiden name is Slaghoople.

ALOHA AND KEEP THE FAITH — rts■

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

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