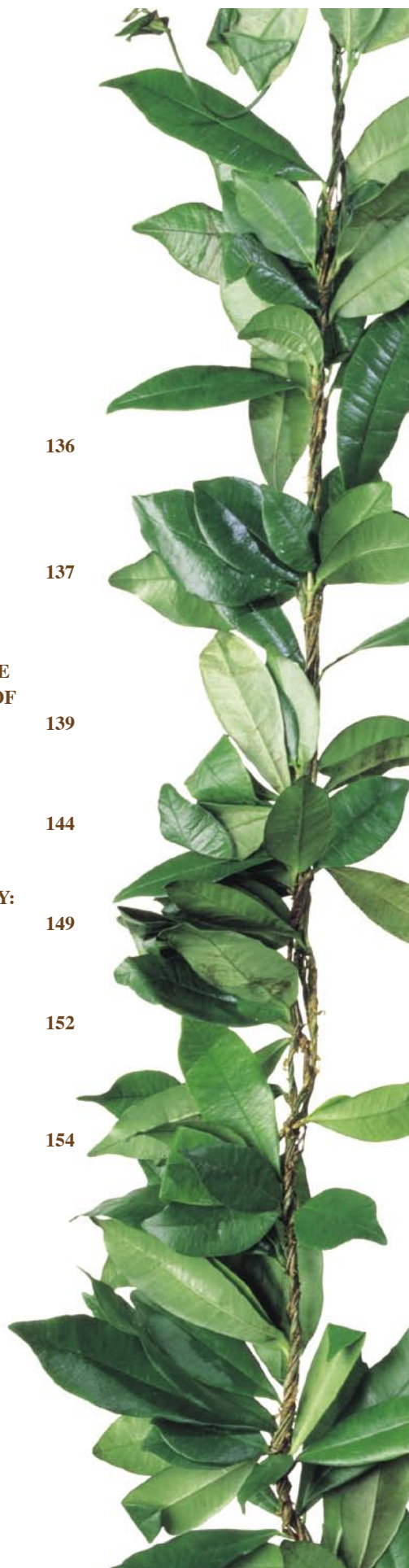


# HAWAI'I MEDICAL JOURNAL

A Journal of Asia Pacific Medicine

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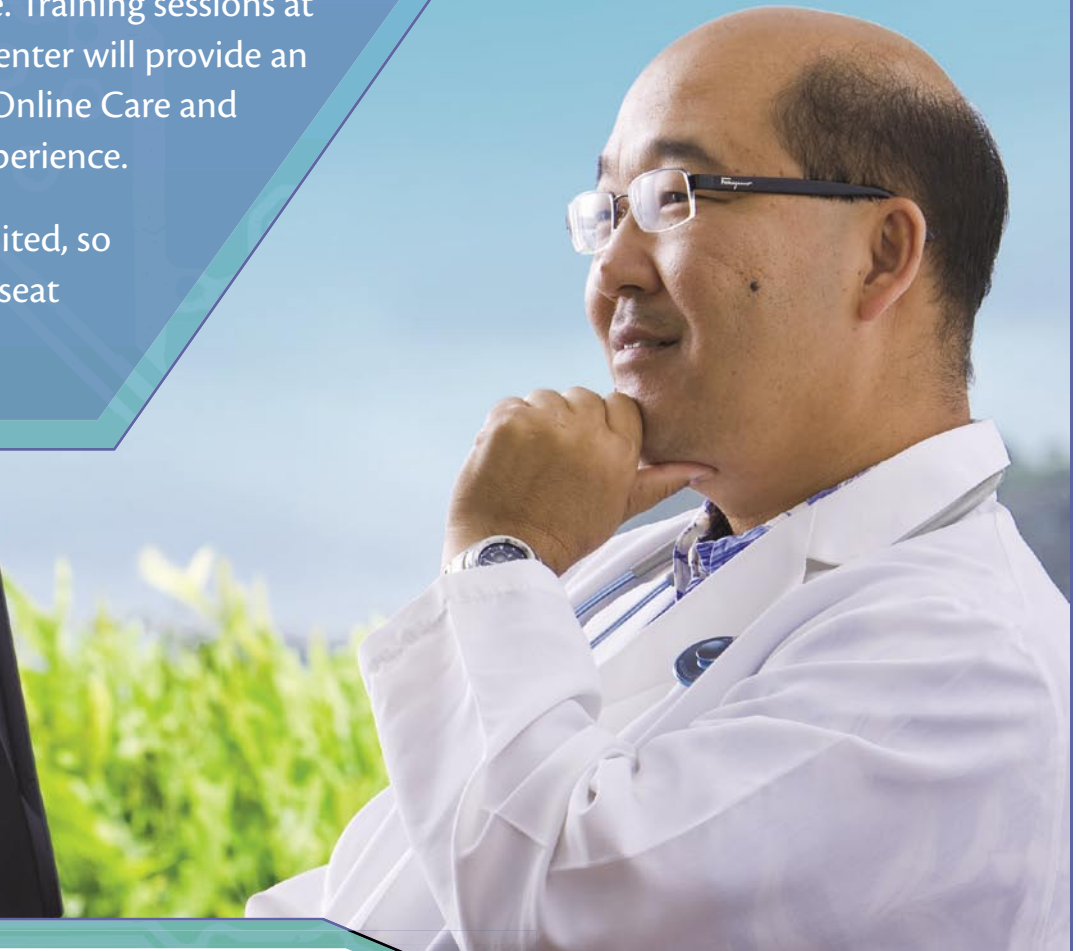
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# HAWAI'I MEDICAL JOURNAL

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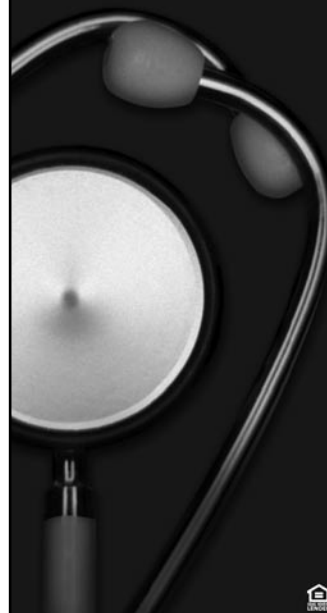
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## Editorial Commentary & Appreciation

Over the last several years, journal editors, ourselves included, have begun to deal with a dichotomy within material submitted for publication. One group of articles is heavily and rigorously evidence based with opinions and conclusions directly limited by, and derived from the presented data, whereas a second and increasingly frequent group, views data collection and interpretation with a much wider and inclusive lens. For example, standard practices for obtaining informed consent may be inappropriate in some populations (ie, group vs individual agreement to consent) and the formulation of conclusions from the available data sets is quite different. Accurate research evaluation of competing therapies, given equipoise, often requires the use of placebo components, yet many object to such use<sup>1</sup> as producing unnecessary risk<sup>2</sup> or limiting the value of such research.<sup>3</sup>

We recognize the potential value of “non traditional” research as well as newly developing group research techniques and will, as objectively as possible, evaluate such material for publication. We continue to expect and require the highest ethical standards in submitted materials.

A note of appreciation and explanation is appropriate at this time. As a peer review journal, we require expert review of submitted materials. We do this, in many cases, by asking the author whom he/she would recommend to review the submission. We do this because we need specific expertise, which is difficult to obtain in our small and geographically isolated state. We seek secondary reviewers if there is any indication of a conflict of interest. We are extremely appreciative of the time and effort many busy physicians, both in academic and private practice, contribute to complete these reviews. We are all in their debt.

*S. Kalani Brady MD and Michael J. Meagher MD; HMJ Co-Editors*

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## ERRATUM

Sugihara N, Watanabe M, Tomioka M, Braun KL, Pang L. Cost–Benefit Estimates of an Elderly Exercise Program on Kaua‘i. *HawaiiMedJ*. 2011;70(6):116-120.

*The calculation on page 118, top of right hand column should read:*

$$(16,389 \times .77) \times 1.093^5 = \$19,685$$





# Cesarean Scar Dehiscence Associated with Intrauterine Balloon Tamponade Placement After a Second Trimester Dilation and Evacuation

Reni Soon MD; Tod Aeby MD; and Bliss Kaneshiro MD, MPH

## Abstract

*While surgical abortion is a safe procedure, the most common complication is excessive bleeding. Methods to conservatively manage hemorrhage are gaining popularity. The authors present a case of a Cesarean scar rupture that occurred after an intrauterine balloon tamponade was placed to treat postabortion bleeding.*

## Introduction

Legal surgical abortion is an extremely safe procedure with a mortality rate significantly lower than live birth.<sup>1,2</sup> The most common complication of a second trimester termination is excessive bleeding, typically due to uterine atony, retained products, uterine or cervical lacerations, or abnormal placentation.<sup>3</sup> The management of these complications depends on the cause, but can include uterotonics, reaspiration, Foley or intrauterine balloon tamponade, uterine artery embolization, hemostatic sutures, or hysterectomy.

In a woman with a prior Cesarean section, additional consideration should be given to scar dehiscence and rupture as a possible cause of bleeding. This complication has been reported with labor induction and induction termination. With the increasing number of Cesarean sections being performed, it is important to recognize the unique challenges presented by this population of women. The authors report a case of Cesarean scar rupture that occurred following a dilation and evacuation procedure in conjunction with intrauterine balloon tamponade placement.

## Case

A 44-year-old healthy gravida 4 para 2 woman presented to our service with a spontaneous abortion at 14-3/7 weeks. The diagnosis had been established by an ultrasound which showed an 88g fetus with absent cardiac activity and a large omphalocele. The patient's history was significant for two previous Cesarean sections and a first trimester spontaneous abortion. Her preoperative hematocrit was 36.3%.

The dilation and evacuation procedure was performed without difficulty under general anesthesia. Immediately following evacuation of all uterine contents, brisk bleeding was noted. Examination of the cervix revealed a small laceration from the tenaculum site that was repaired. Bleeding continued from the uterus and uterine atony was noted which was treated with bimanual uterine massage, reaspiration and 0.2 mg of intramuscular methylergonovine. There was improvement in both uterine tone and bleeding. An intraoperative ultrasound revealed an empty uterine cavity and no extrauterine fluid collection. Estimated blood loss at this time was 1000 mL and postoperative hematocrit was 28.7%.

The patient was admitted for observation and over the next 6 hours vaginal bleeding was minimal. However, labwork drawn 6 hours postoperatively revealed a hematocrit of 17.8% and a mild coagulopathy. On examination, the patient had abdominal tenderness, and a 20-week size uterus was palpated. The patient was transfused with whole blood and fresh frozen plasma and was taken back to

the operating room. Five hundred milliliters of hematometra was evacuated with suction. A Foley bulb was inserted into the uterine cavity and filled with 120 mL of normal saline. An intraoperative ultrasound confirmed intrauterine placement of the Foley bulb.

Following this procedure, the patient had minimal vaginal bleeding but continued to have abdominal pain. Despite the absence of vaginal bleeding, serial labwork revealed a slow decrease in hematocrit level over the following 12 hours. An ultrasound done 12 hours after the second procedure was suspicious for blood clots both inside and outside the uterine cavity.

The patient was taken back to the operating room and a laparoscopy was performed. Upon entry into the abdomen, dense adhesions were encountered and the procedure was converted to a laparotomy. Extensive lysis of adhesions revealed the vesicouterine peritoneum to be intact and covering a large amount of blood clot. Upon entry into the vesicouterine peritoneum, brisk bleeding ensued and a uterine defect at the site of the cesarean section scar was identified. This dehiscence extended laterally across the anterior aspect of the uterus. Because of the extent of the defect and the continued bleeding, a hysterectomy was performed. Estimated blood loss for this procedure was 2000 mL and the patient received transfusions of blood, platelets, and fresh frozen plasma. She recovered without any further incident and was discharged home on postoperative day 4. Finally pathology of the uterus reported no placenta accreta.

## Discussion

Occurring in approximately 1.4% of cases, bleeding is the most common complication in second trimester terminations. After uterotonics, oftentimes uterine conserving procedures such as intrauterine tamponade or uterine artery embolization are attempted before proceeding to laparotomy. As demonstrated with this case, in a patient who has had a Cesarean section, uterine rupture or uterine dehiscence should also be considered. With the Cesarean delivery rate increasing for the 11th consecutive year in 2007,<sup>4</sup> women who have had a cesarean section constitute a rapidly growing population. Cesarean deliveries accounted for 31.8% of all births in 2007, and this rate has increased by more than 50% since 1996 when they were 20.7% of all births.<sup>4</sup> Recognizing any complications unique to this population is vital to the care and management of these patients.

The safety of a dilation and evacuation after a previous Cesarean section has been documented. In a series of 1064 patients who underwent second trimester dilation and evacuation, 70 patients had a previous uterine scar and there were no major complications.<sup>5</sup> Another recently published series reported on 91 patients with previous Cesarean sections who had undergone dilation and evacuation, and there were no cases of uterine perforation or other major complication.<sup>6</sup> In 2004 Lichtenberg and Frederiksen<sup>7</sup> reported two cases of Cesarean scar dehiscence after a second trimester dilation and evacuation. The authors reported that a separation of the myometrium that anatomically matches a previous uterine scar, especially in the

presence of an intact serosa or vesicouterine peritoneum, is most likely a dehiscence rather than an iatrogenic injury that occurred at the time of uterine evacuation.

In the management of hemorrhage following either a delivery or a termination of pregnancy, the successful utilization of intrauterine tamponade techniques has also been well-described. For many years uterine packing was the primary technique employed.<sup>8</sup> In 1985 Bowen and Beeson<sup>9</sup> described two cases of postpartum hemorrhage in which Foley catheter balloons were inflated in the lower segment of the uterus for tamponade. The Sengstaken-Blakemore esophageal tube,<sup>10</sup> the Rusch urological catheter,<sup>11</sup> and the condom catheter<sup>12</sup> have also been used in cases of postpartum hemorrhage that were unresponsive to uterotonics. Perhaps the most cited method has been the Bakri intrauterine balloon<sup>13</sup> which was developed in 1999 specifically for the postpartum uterus. One case series found intrauterine tamponade with balloon catheters to be 90% effective in the management of postpartum hemorrhage.<sup>14</sup> Foley catheter balloons were utilized successfully after a second trimester dilation and evacuation procedure<sup>15</sup> and the Bakri intrauterine balloon effectively controlled refractory bleeding after a first trimester<sup>16</sup> and a second trimester abortion procedure.<sup>17</sup> Several authors have also demonstrated the role of intrauterine tamponade in the management of cervical pregnancies.<sup>18-22</sup>

Intrauterine balloon tamponade has also been described in non-obstetric settings. It has been utilized to control bleeding after operative hysteroscopy,<sup>23</sup> uterine evacuation for gestational trophoblastic disease,<sup>24</sup> cold-knife cone biopsy,<sup>25</sup> and for profound dysfunctional uterine bleeding.<sup>26</sup>

In the present case, the authors describe an unsuccessful attempt at balloon tamponade for bleeding after a second trimester dilation and evacuation. The authors suspect that a dehiscence of the Cesarean scar occurred either at the time of the original evacuation procedure, with aspiration of hematometra, or following Foley bulb expansion. Based on ultrasounds performed between each of the procedures, it is most likely that the dehiscence occurred with aspiration of the hematometra. With the Foley bulb in place, the authors suspect that this defect was extended significantly.

It is also possible, that a perforation, rather than a dehiscence occurred with one of the aspiration procedures. However, similar to the cases published by Lichtenberg and Frederiksen,<sup>7</sup> the serosa of the uterus was intact, and the dilation and evacuation procedure was performed by a skilled provider with more than 20 years of experience.

While a dilation and evacuation procedure after a previous Cesarean section is safe, in the setting of postabortion bleeding complications, uterine dehiscence and perforation must be strongly considered. If suspected, a diagnostic procedure such as laparoscopy should be performed prior to placement of intrauterine balloon tamponade devices. Failure to do so can lead to significant extension of defects if they are present.

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# Dual Paraneoplastic Syndromes: Small Cell Lung Carcinoma-related Oncogenic Osteomalacia, and Syndrome of Inappropriate Antidiuretic Hormone Secretion: Report of a Case and Review of the Literature

Ekamol Tantisattamo MD and Roland C.K. Ng MD

## Abstract

*Acquired isolated renal phosphate wasting associated with a tumor, known as oncogenic osteomalacia or tumor-induced osteomalacia, is a rare paraneoplastic syndrome caused by overproduction of fibroblast growth factor 23. Oncogenic osteomalacia is usually associated with benign mesenchymal tumors. Syndrome of inappropriate antidiuretic hormone secretion (SIADH), on the other hand, is a common paraneoplastic syndrome caused by small cell carcinoma (SCC). Concomitant oncogenic osteomalacia and SIADH associated with SCC is very rare with only 4 other cases reported in the literature. The authors report a case of small cell lung cancer (SCLC)-related renal wasting hypophosphatemia and concurrent SIADH, and review the literature reporting 9 other cases of SCC associated with oncogenic osteomalacia. Almost half of reported cases of renal phosphate wasting associated with SCC concomitantly presented with SIADH. These cases had initial serum phosphorus level lower and survival periods shorter than those without SIADH. This rare combination of a dual paraneoplastic syndrome and low serum phosphorus may be a poor prognostic sign. In addition, both renal phosphate wasting and SIADH usually occur in a short period of time before identification of SCC. Therefore, renal wasting hypophosphatemia with concomitant SIADH/hyponatremia should prompt a search for SCC rather than a benign mesenchymal tumor.*

## Introduction

Paraneoplastic syndrome is a condition caused by tumors secreting substances which result in a variety of clinical syndromes. Oncogenic osteomalacia, also known as tumor-induced osteomalacia, is a rare metabolic bone syndrome presenting as a paraneoplastic syndrome of isolated renal phosphate wasting, and is usually caused by benign mesenchymal tumors.<sup>1</sup> However, this paraneoplastic syndrome has also been reported to be associated with malignant tumors. As far as the authors are aware, there are 9 previously reported cases of renal hypophosphatemia associated with small cell carcinoma (SCC).<sup>2-9</sup> The authors report one new case of concomitant renal wasting hypophosphatemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with small cell lung cancer (SCLC), and review the literature on the 9 cases of renal hypophosphatemia associated with SCC.

## Case Report

A 60-year-old Caucasian man with a history of type 2 diabetes, hypertension, hyperlipidemia, gout, and 80-pack-years smoking presented with chronic hyponatremia starting on March 2007. He refused hospitalization and had persistent hyponatremia ranging from 117 to 130 mEq/L despite fluid restriction for a few months. Two months later, he was admitted with nausea, vomiting, and generalized malaise. His serum sodium was 119 mEq/L. Laboratory workup confirmed SIADH: euvolemic hypotonic hyponatremia with serum osmolality of 249 mOsm/kg, high urine sodium of 105 mEq/L, high urine osmolality of 680 mOsm/kg, normal thyroid function with TSH of 0.77  $\mu$ IU/mL (normal range 0.30 – 6.60  $\mu$ IU/mL), normal adrenal

function - morning serum cortisol level of 29.4  $\mu$ g/dL (normal range 6.0 – 22.4  $\mu$ g/dL), BUN 4 mg/dL, and serum creatinine 0.6 mg/dL. The patient was treated with fluid restriction, intravenous 3% NaCl, salt tablets, and demeclocycline. His symptoms of hyponatremia improved, but his serum sodium remained low.

In addition, he was found to have persistent hypophosphatemia (serum phosphorus of 1.2 mg/dL). Fractional excretion of phosphorus was 41% (normal < 5%). Other laboratory findings: Serum calcium and albumin were 9 mg/dL and 3.8 g/dL respectively, urine glucose was 2+, alkaline phosphatase was 117 IU/L (normal range 30 – 120 IU/L), 1,25-dihydroxy vitamin D (1,25(OH)<sub>2</sub>D) was 16 pg/mL (normal range 15 – 60 pg/mL), and total 25-hydroxy vitamin D (25(OH)D<sub>3</sub>) was 34 ng/mL (normal range 20 – 100 ng/mL). These data support isolated renal phosphorus wasting not due to vitamin D deficiency. He had no family history of renal disease, bone disease, or cancer. He was treated with phosphorus supplementation; however, his serum phosphorus remained low.

Chest X-ray was unremarkable. However, because of a high suspicion for lung cancer, chest computed tomography (CT) scan was done, and showed a 2 cm focal irregular density in the left lung apex and 6.2x4 cm mediastinal mass extending to the left hilum. Bronchoscopy with aspiration and biopsy confirmed SCLC. Abdominal CT scan showed multiple hepatic hypodense masses suspicious for metastases. Bone scan showed no abnormal foci suggestive of metastasis to the skeleton. During the workup for metastases, the patient continued to have hyponatremia (serum sodium 122 - 129), hypophosphatemia (phosphate 1.2 – 1.5), fatigue, and low back pain.

Small cell lung cancer with liver metastases was diagnosed, and chemotherapy with cisplatin and irinotecan was started. After the first cycle of chemotherapy, his serum sodium was still low, but his serum phosphorus increased to 4.5 mg/dL. Two weeks after chemotherapy, he developed severe diarrhea, pancytopenia, and subsequently septic shock with multi-organ failure requiring vasopressors and increasing ventilator support. He expired one and a half months after the diagnosis of SCLC. Autopsy was not performed.

## Review of Literature

The data of the 9 previously reported cases of renal hypophosphatemia-related SCC and of this current case is shown in the Tables 1 and 2. Among these 10 cases reported with oncogenic osteomalacia, five cases had additional paraneoplastic syndrome (4 cases with SIADH, and 1 case with Cushing's syndrome), and one case had two additional paraneoplastic syndromes with SIADH and Cushing's syndrome. SCC occurred at pulmonary sites in 8 cases. The other 2 cases had SCC in extrapulmonary sites: cervical lymph node and urinary bladder. The patients' ages at the time of study ranged between 37 and 72 years. The mean age was 57.8 years. Eight cases were men, and two cases were women.



Table 1. Clinical information of the 9 previously reported cases and of the authors' patient with renal wasting hypophosphatemia associated with SCC

Patient number	Age (years) / Gender / Ethnicity	History of smoking	Symptoms / Duration before the onset of hypophosphatemia	Paraneoplastic syndrome(s)	Site of the primary tumor / Site(s) of the tumor metastasis / Treatment	Bone biopsy	Cause of death / time until death after the onset of hypophosphatemia
2	56 / Female / African-American	NA	Weakness, diffuse body aches and nausea. Temporal wasting/1 month	Fanconi +/- SIADH	Pulmonary / Bone marrow / Chemotherapy	NA	Gram negative septicemia during pancytopenia / 20 months
3	69 / Male	NA	Dysuria, hematuria, urinary frequency, and nocturia / 1 month	Hypophosphatemia	Urinary bladder (Kultschitzky-type cell) / No evidence / Surgery	Not Done	Loss to F/U 15 mo from the onset of hypophosphatemia
4	57 / Male	Yes	Nontraumatic tarsal pain of both feet. Hemoptysis 2 times / 1 month	Phosphate diabetes	Pulmonary / Tarsal and iliac bones / Chemotherapy and radiotherapy	Strongly suggestive of osteomalacia	NA / 10 months
5	37 / Male	NA	Mild dysphagia, weight-loss, hemoptyses, and pain affecting the lumbar spine, buttocks, and thighs	Renal phosphate wasting and SIADH	Pulmonary / Not available / Chemotherapy	NA	NA / 15 months
6	57 / Male	NA	Nausea, polyuria, weakness / 1 month (SIADH started first)	Oncogenic osteomalacia and SIADH	Pulmonary / Liver, thoracolumbar spine / Pneumonectomy	Osteomalacia	NA / 3 months
Authors' Patient	60 / Male / Caucasian	80 packs per year	Nausea, vomiting, generalized malaise and weakness / 2 months (SIADH started first)	Renal phosphate wasting and SIADH	Pulmonary / Liver / Chemotherapy	Not Done	Pancytopenia, septic shock with multi-organ failure / 1.5 months
7	72 / Male	1 pack per day, many years	Chest pain and weight-loss / Same	Renal phosphate wasting and SIADH	Pulmonary / No further work-up due to the patient deteriorated rapidly / No	No	NA/ Same period
8	58 / Female	NA	Dysphagia, epigastric pain, weight-loss (1 stone) / 12 months	Oncogenic osteomalacia and Cushing's syndrome	Trachea / Lymph nodes, liver, pancreas, adrenal glands, vertebrae / Esophagectomy	Osteomalacia	NA / 1 month
9	46 / Male	NA	Back pain, cervical adenopathy / Same	Renal phosphate wasting, SIADH and Cushing's syndrome	Extrapulmonary / Bone / Chemotherapy	Not Done	NA / 10 months

NA = Not available

Table 2. Laboratory data of the 9 previously reported cases and of the authors' patient with renal wasting hypophosphatemia associated with SCC

Patient number	Serum phosphorus (mg/dL) (N: 2.5-4.5)		TmP/GFR (mg/dL)	Serum sodium (mEq/L)		Serum cortisol (µg/dL)
	Initial	After tumor treatment		Initial	After tumor treatment	
2	2.2	3.4	NA	132	141	NA
3	1.9	2.7	NA	NA	NA	NA
4	1.36	1.55	0.8	NA	NA	NA
4	1.95	3.75	1.1	NA	NA	NA
5	1.5	NA	Very low	113	No	21 (AM)
6	1.2	Still low	NA	107-	138	17.3
Authors' Patient	1.2	4.5	0.6	117	127	29.4 (AM)
7	0.84	NA	0.4	117	NA	NA
8	0.99	1.08	0.5	143	143	45.38 at 9 am
9	1.2	4.3 -> 1.2-2.8	1.40	107	Corrected and recurrence	35

NA = Not available

The most common presenting symptoms included generalized weakness and musculoskeletal pain. Cervical spinal pain occurred in two cases. Back pain occurred in three cases. Two cases with SCC in the bronchus and trachea had dysphagia. Nine cases had hypophosphatemia before the diagnosis of SCC, but two cases with symptomatic hyponatremia were initially diagnosed with SIADH and were subsequently found to have hypophosphatemia. Two cases developed Cushing's syndrome after hypophosphatemia occurred. Mediastinal lymph node metastases occurred in four cases, and seven cases had distant metastases to brain, visceral pleura, liver, pancreas, adrenal glands, and bone (spine, iliac bone). Three cases had no documented metastasis.

Bone biopsy was reported in four cases. The results from the bone biopsy in two cases showed evidence of osteomalacia, and those from another two cases showed evidence of osteomalacia with increased osteoid. Regarding phosphate excretion, maximum tubular resorption of phosphorus factored for GFR (TmP/GFR) was decreased in six cases (range 0.4 to 1.1 mg/dL), was very low in one case (no value reported), and was not reported in three cases. 1,25 dihydroxycholecalciferol (1,25(OH)<sub>2</sub>D) was reported in five cases. Two cases had low 1,25(OH)<sub>2</sub>D, and three cases, including this case, had low normal 1,25(OH)<sub>2</sub>D levels. Fibroblast growth factor (FGF 23), which causes phosphate wasting and is currently thought to be pathogenic in this syndrome, was not reported in any of the cases. In this case, FGF 23 was requested to be sent to a commercial laboratory, but somehow the test was never sent.

Among the ten cases, nine cases received chemotherapy, radiation therapy, and/or surgery. After treatment, serum phosphorus returned to normal in five cases; however, one case had hypophosphatemia recurring after tumor recurrence in conjunction with the presentation of Cushing's syndrome. Serum phosphorus after treatment was not reported in one case. Three of the nine treated cases continued to have persistent hypophosphatemia (1 case after chemotherapy and radiation and two cases after pneumonectomy and esophagectomy). In the one case in which no treatment was given, the patient expired shortly after diagnosis of SCC, and serum phosphorus was not reported before the patient expired.

Among the five cases with concomitant SIADH (one case had both SIADH and Cushing's syndrome), three cases received chemotherapy and/or radiation therapy. Of those three cases, one case had initial resolution of hyponatremia, but the hyponatremia recurred after the tumor recurrence with Cushing's syndrome. Two cases had persistent hyponatremia despite fluid restriction, hypertonic saline, oral sodium tablets, or demeclocycline.

Nine out of ten cases expired. One case reported the cause of death as gram-negative septicemia. This current case had septic shock, pancytopenia, and multi-organ failure after the first cycle of chemotherapy. One case was lost to followup after fourteen months from the diagnosis of SCC of urinary bladder.

Most patients developed the paraneoplastic syndromes, oncogenic osteomalacia and/or SIADH, shortly (not more than 2.5 months for oncogenic osteomalacia and 3.5 months for SIADH) before the diagnosis of SCC. However, a minority developed the paraneoplastic syndromes after diagnosis of SCC (one patient had SIADH three weeks after the SCC diagnosis, and two other patients developed Cushing's syndrome after the diagnosis of SCC). One of these patients presented with hypophosphatemia and oncogenic osteomalacia as long as one year after the SCC diagnosis.

When the one case that was lost to follow-up is excluded, the time until death extended up to 20 months after presenting with hypophosphatemia and the syndrome of oncogenic osteomalacia. Seven out of ten cases had documented distant metastases. Survival did not exceed 20 months after presenting with hypophosphatemia. In four SCC cases presenting with only renal phosphate wasting, initial serum phosphorus ranged between 1.36 and 2.2 mg/dL, and this group had survival ranging between 8 to 20 months. On the other hand, in the four SCC cases presenting with both tumor-induced renal phosphate wasting and SIADH, initial serum phosphorus tended to be more severe between 0.84 and 1.5 mg/dL and initial serum sodium ranged between 107 and 117 mmol/L. Survival in this group was much shorter- only five and four months after presentation with hypophosphatemia and SIADH, respectively. There was no correlation between survival period and normalized serum phosphorus or serum sodium after the treatment of SCC.

In addition to co-existent dual paraneoplastic syndromes of oncogenic osteomalacia and SIADH, there are two cases of SCC associated with oncogenic osteomalacia and Cushing's syndrome.<sup>8,9</sup> One case had a primary tumor in the trachea. Another case had metastatic extrapulmonary SCC, and, interestingly, had triple paraneoplastic syndromes (oncogenic osteomalacia, SIADH, and Cushing's syndrome). Both cases had distant metastases, and developed ectopic corticotropin (adrenocorticotrophic hormone [ACTH]) production after renal phosphate wasting developed. They had hypokalemia, high serum and urine cortisol levels, elevated ACTH levels, and lack of suppression with dexamethasone which was consistent with Cushing's syndrome secondary to ectopic ACTH production likely from SCC.

## Discussion

Paraneoplastic syndrome is a condition caused by tumors secreting substances which result in a variety of clinical syndromes. SIADH is probably the most common paraneoplastic syndrome in the patient with SCLCs. On the other hand, oncogenic osteomalacia is a rare metabolic bone syndrome presenting as a paraneoplastic syndrome of isolated renal phosphate wasting, and is usually caused by benign mesenchymal tumors.<sup>1</sup> Oncogenic osteomalacia occurs with a malignant tumor in only 10% of cases, and thus the dual combination with SIADH is extremely rare. However, from this review, five out of 10 cases of renal phosphate wasting associated with SCC also presented with SIADH.

Tumor-associated SIADH results from inappropriate secretion of antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), from some tumors. SCLCs, which are neuroendocrine tumors, can express the arginine-vasopressin-neurophysin II (AVP-NP II) gene increasing AVP production.<sup>10</sup> AVP controls AVP-regulated water channels called aquaporin-2,<sup>11</sup> located on the luminal membrane of principal cells of cortical and medullary collecting tubules, and causes water reabsorption into the cell and then interstitium.<sup>1</sup> SCLCs account for 75% of cases of SIADH caused by tumors.<sup>12</sup>

Oncogenic osteomalacia, also known as tumor-induced osteomalacia, is a rare paraneoplastic syndrome frequently associated with mesenchymal tumors of mixed connective tissue in the bone or soft tissue.<sup>13</sup> The most common sites of tumors causing oncogenic osteomalacia are osseous (55% long bone, 30% head and neck, and 20% upper extremities), soft tissue including skin (66% in the lower

extremities).<sup>13</sup> However, 10% of cases are due to malignant tumors and 5% are from tumors from multiple sites.<sup>14</sup> Reported malignant tumors associated with oncogenic osteomalacia include prostatic cancer,<sup>15</sup> multiple myeloma,<sup>16</sup> small cell carcinoma of the lungs,<sup>2, 4-6, 9</sup> the urinary bladder,<sup>3</sup> and extrapulmonary lymph nodes.<sup>8</sup> These tumors highly express the FGF23 gene producing FGF23 which has phosphaturic and inhibitory 1- $\alpha$ -hydroxylase activities. An increase in levels of FGF23 causes decreased expression of sodium-phosphorus cotransporters in the proximal tubules of the kidney which then results in decreased renal phosphate reabsorption. The inhibitory effect of FGF23 on 1- $\alpha$ -hydroxylase also leads to decreased production of 1,25(OH)<sub>2</sub>D which then causes a decrease in intestinal phosphorus absorption which potentiates the hypophosphatemia. Low levels of 1,25(OH)<sub>2</sub>D also stimulate parathyroid hormone (PTH) secretion, which contributes to decreased renal phosphorus reabsorption.<sup>1</sup> Mobilization of phosphorus from skeleton over a long period of time then results in osteomalacia. Even though markedly elevated FGF23 is pathogenic in oncogenic osteomalacia and can be a marker of oncogenic osteomalacia.<sup>17, 18</sup> Elevated levels of FGF23 can also be found in other diseases such as X-linked hypophosphatemia (XHP) and chronic kidney disease.

Renal phosphate wasting can be divided into congenital and acquired conditions. Two rare inherited diseases causing isolated renal phosphate wasting are X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR).<sup>19, 20</sup> The patients with these two disorders present in childhood and have a familial history.

The most common cause of acquired renal phosphate wasting is primary hyperparathyroidism.<sup>20</sup> Oncogenic osteomalacia is a rare cause of acquired renal phosphate wasting, which mostly occurs in adults with an average age of 33 years (range between age 7 to 73).<sup>13</sup> The onset of oncogenic osteomalacia may precede the diagnosis of tumor with a range between 3 months to 17 years.<sup>14</sup> Clinical manifestations of oncogenic osteomalacia include biochemical findings and bone abnormalities. Chronic hypophosphatemia causes a deficiency in osteoid mineralization and osteomalacia. In addition to hypophosphatemia, other biochemical features include renal phosphate wasting, low 1,25(OH)<sub>2</sub>D levels, increased alkaline phosphatase, and normal calcium, parathyroid hormone (PTH), calcitonin, and 25(OH)D<sub>3</sub> levels.<sup>13</sup> Patients with oncogenic osteomalacia often present with the symptoms of osteomalacia; bone pain, muscle pain, or recurrent fractures.<sup>1</sup> Stress fractures can occur as pseudofractures, or Looser-Milkman lines, which are the typical radiological findings of oncogenic osteomalacia.<sup>13</sup>

In the authors' patient, hypophosphatemia was found at the time of diagnosis of SCLC. He had the typical biochemical features including hypophosphatemia from documented renal phosphate wasting, low normal 1,25(OH)<sub>2</sub>D, high normal alkaline phosphatase, and normal calcium and 25(OH)D<sub>3</sub> levels. However, there were no radiological findings of osteomalacia. He had hypophosphatemia 1.5 months before death, so the duration of hypophosphatemia may have been too short to develop radiographic changes.

The most definitive diagnostic criterion of oncogenic osteomalacia is reversal of biochemical abnormalities following tumor resection. However, most of the time, oncogenic osteomalacia results from slow growing mesenchymal tumors some of which are very small and may not be detected from screening imaging. As a consequence,

localization of the tumor is difficult.<sup>21</sup> Ito N et al, reported the usefulness of systemic venous sampling of FGF 23 from specific large venous vessels (eg, subclavian, internal jugular, brachiocephalic, superior vena cava, inferior vena cava, common iliac, external iliac, internal iliac, and femoral veins) in order to guide and select the possible location of tumor where the imaging (CT scan and/or MRI) should be directed. They found that venous sampling with the highest FGF 23 level suggested the location of responsible tumors in 8 out of 10 cases.<sup>22</sup>

Systemic venous sampling of FGF 23 is not a general test, but it can be safely performed with interventional radiology. However, it may not always identify the responsible tumor which is distal to the vein having the highest FGF 23 level. The reliability of the test depends on the technique, how selectively blood samples are collected, the location of the tumor, and the rate of FGF 23 secretion from the responsible tumor.<sup>23</sup> In addition to identifying the location of tumor, FGF 23 can be used to monitor response to treatment since the level will decrease rapidly after tumor resection.<sup>24</sup>

In the authors' patient, because SCLC is an aggressive and generally incurable malignant tumor, it is difficult to prove the causal relationship between SCLC and renal phosphate wasting by complete removal of SCLC. However, the clinical features of acquired renal phosphate wasting in the authors' patient are compatible with oncogenic osteomalacia, and his serum phosphorus normalized after the first cycle of chemotherapy, suggesting that the renal phosphate wasting in the authors' patient was likely due to oncogenic osteomalacia associated with SCLC.

The appearance of SIADH in SCLC does not correlate with chemotherapy or survival.<sup>25</sup> On the other hand, from Table 1, seven out of 10 cases of SCC with renal phosphate wasting had distant metastases, and survival in those also presenting with SIADH was shorter than the group with only renal phosphate wasting. The average initial serum phosphorus level was lower in the patients with combined SIADH. In SCC, renal phosphate wasting associated with concomitant SIADH, as well as the lower initial serum phosphorus, may be a poor prognostic sign or a marker of terminal SCC. Therefore, a high index of suspicion should be raised in patients with both acquired renal phosphate wasting and SIADH and should prompt an investigation for underlying malignancy, especially SCLC, rather than a benign mesenchymal tumor as in most cases of oncogenic osteomalacia.

Oncogenic osteomalacia and Cushing's syndrome were co-existent in two patients who expired shortly after Cushing's syndrome was diagnosed. The short survival periods in these patients may be due to a poor prognosis of SCLC especially when it is associated with ectopic ACTH production<sup>26</sup> and low initial serum phosphorus.

Symptoms of SIADH depend on the severity of hyponatremia and especially the rate of decrease in serum sodium. Many patients with SIADH are relatively asymptomatic because the hyponatremia developed gradually. Patients with oncogenic osteomalacia may present with pain or musculoskeletal problems, or an abnormal bone x-ray. Treatment of oncogenic osteomalacia usually consists of surgically removing a benign mesenchymal tumor, which results in complete resolution of signs and symptoms. However, if the tumor is not totally removed or malignant tumors are not completely treated, symptoms and signs of hypophosphatemic osteomalacia will remain. In such a case, symptomatic treatment with phosphorus

replacement and calcitriol can be used to alleviate the symptoms of hypophosphatemia such as pain and weakness.

## Conclusion

Paraneoplastic SIADH is commonly associated with SCLC, but oncogenic osteomalacia is rarely found in patients with SCLC. Dual paraneoplastic syndromes, oncogenic osteomalacia and SIADH, are even more uncommon.

In almost half of the nine reported cases of oncogenic osteomalacia associated with SCC, the patients concomitantly presented with SIADH. These patients had lower initial serum phosphorus levels and shorter survival periods than those without SIADH. The presence of dual paraneoplastic syndromes with a very low serum phosphorus may be a poor prognostic sign. In addition, renal phosphate wasting and hyponatremia usually appear in a short period of time before identification of SCC. Therefore, an expedited work-up for a malignant lung tumor, rather than a benign mesenchymal tumor, should be pursued in the adult who presents with both oncogenic osteomalacia and SIADH.

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# Koch's Postulates, Carnivorous Cows, and Tuberculosis Today

Frank L. Tabrah MD

## Abstract

*With Koch's announcement in 1882 of his work with the tubercle bacillus, his famous postulates launched the rational world of infectious disease and an abrupt social change—strict patient isolation.*

*The postulates, so successful at their inception, soon began to show some problems, particularly with cholera, which clearly violated some of Koch's requirements. Subsequent studies of other diseases and the discovery of entirely new ones have so altered and expanded the original postulates that they now are little but a precious touch of history. The present additions and replacements of the original concepts are skillful changes that several authors have devised to introduce new order into understanding complex viral and prion diseases. In 1988, this knowledge, with the totally rational response of the British population and its cattle industry, was critical in promptly blocking the threatened epidemic of human prion disease.*

*In contrast, the recent upsurge of tuberculosis (TB) in the worldwide AIDS epidemic in developing countries, and the sudden increase in metabolic syndrome in wealthy ones, suggests the need for focused sociobiologic research seeking ways to affect the damaging lifestyle behavior of many less educated populations in both settings. The world awaits an equivalent of Koch's Postulates in sociobiology to explain and possibly avert large self-destructive behaviors.*

On 24 March 1882, a bitter cold night in Berlin, Dr. Robert Koch, speaking to the Berlin Physiological Society, a small group of savants that included the great European pathologist, Virchow, offered these words:

There have been repeated attempts to fathom the nature of tuberculosis, but thus far without success. The so frequently successful staining methods for the demonstration of pathogenic microorganisms have failed in regard to this disease, and to date, the experiments designed to isolate and cultivate a tubercle virus cannot be considered successful, so that... the direct demonstration of the tuberculous virus is a still unsolved problem.

Within the hour, world history was to be made by Koch's words about his isolation and transfer of specific organisms and resulting disease:

The aims of the study had to be directed toward the demonstration of some kind of parasitic forms which are foreign to the body and which might possibly be interpreted as the cause of the disease. This demonstration became successful, indeed, by means of a certain staining process, which disclosed characteristics and heretofore unknown bacteria in all tuberculous organs.

Koch closes with the description of his remarkable staining process:

With the exception of leprosy bacilli, all other bacteria which I have thus far examined assume a brown color with this staining method. The color contrast between the brown stained tissue and the blue tubercle bacilli is so striking that the latter which are frequently present only in very small numbers, are nevertheless seen and identified with the greatest certainty.<sup>1</sup>

With this critical discovery, Koch was able to methodically work out the role of these organisms in the development of tubercles and widespread tissue destruction, and recognize them as the cause of the characteristic pathology of tuberculosis in man, cattle, hogs, chickens, monkeys, and "172 guinea pigs, 32 rabbits, and 5 cats." Meticulous isolation of colonies over many weeks, and transfer of the organisms with characteristic resulting disease led to the famous Henle-Koch Postulates which at the time became the gold standard for proof relating a parasitic organism with a specific disease:

1. The organism must be shown to be invariably present in characteristic form and arrangement in the diseased tissue.
2. The organism, which from its relationship to the diseased tissue appears to be responsible for the disease, must be isolated and grown in pure culture.
3. The pure culture must be shown to induce the disease experimentally.
4. The organism should be re-isolated from the experimentally infected subject (this postulate was added after Loeffler).

In contrast with these brilliant disclosures, the century was coming to its end with tuberculosis widely regarded as an inevitable wasting disease which was thought to produce in its victims a refinement of the body, heightened artistic sensibilities, and ennoblement of the soul, notions that were romanticized in the arts and music of the nineteenth century. Mimi's death in Puccini's *La Boheme* and Satine in *Moulin Rouge* are only two of the dozens of TB nineteenth century celebrity deaths, including Guy De Maupassant (1893), Robert Louis Stevenson (1894), and Anton Chekov, a famous writer and physician, 1904.<sup>2</sup>

Despite delay and uncertainty led by Virchow's lifelong skepticism, Koch's work slowly changed the romantic perception of consumptive patients as tragically beautiful victims of a wasting disease to dangerously infectious carriers whose cough or sputum transferring as few as ten bacilli could be an ultimately fatal contact.

With this simple fact in hand, over time, public health measures were put in place involving isolation in sanatoria, masks, sputum, and the lowly spittoon. Although transmission was reduced, successful treatment lay far in the future.

Sheila Rothman, in her 1994 book, *Living In The Shadow of Death*, said:

A generation of physicians, social reformers, and philanthropists were convinced that confining the tubercular [insanatoria] would promote not only societal well-being by isolation of those with the disease, but also well-being by implementing a therapeutic regime. The sanatorium satisfied both the drive to coerce and cure. As concepts of bacteriology gained acceptance, the idea of caring for patients in a setting removed from the general populace was considered wise and necessary to prevent spread of the disease.<sup>3</sup>

Fresh air, rest, and good food were intuitively deemed important. Supplanting the sanatorium routine was the practice of “resting the lung” by pneumothorax. Collapsing the lung by introducing air into the pulmonary cavity was used successfully in 1834 after George Baglivi, in 1696, noted a general improvement in a tubercular patient who suffered a sword wound to the chest. With the wide establishment of sanatoria, and their often heroic routines of cold air, absolute rest and ultimately, thoracoplasty, even under the best conditions in the early nineteenth hundreds, fifty percent of those who entered were dead within five years.<sup>4</sup>

Although transmission of the disease was somewhat abated after Koch’s definitive announcement of mycobacterial spread, the carnage continued into the twentieth century. Today, one hundred years later, through ignorance, poverty, apathy, and the deadly interaction of TB with HIV, the disease continues to kill roughly 5000 people every day, nearly two million a year, making it the second leading cause of adult death by infectious disease,<sup>5</sup> despite the discovery after 1944 of effective antibiotics. Resistance of tubercle bacilli to multidrug regimes has become a serious problem, ironically matching the resistance of patients to treatment of their disease through their refusal or inability to follow their medication regime. Directly observed therapy (DOT) has been successful in several settings<sup>6</sup> with reported results of cure in as high as ninety five percent of cases.<sup>7</sup>

Aside from the effects of specific treatment, there has been a long history of controversy over whether specific public health actions limiting modes of bacterial transmission, such as mandatory reporting and isolation of patients, have been as effective in reducing case incidence as social and economic changes, reduction of poverty, improved housing and nutrition. A comprehensive review of this question will be found in reference eight, which is much more than an academic argument, as conclusions can affect future resource allocation for disease control.

## **Tuberculosis and AIDS**

People who are infected with HIV are especially susceptible to developing active TB. TB is the leading cause of death among people-living-with-HIV/AIDS (PLWHA) and one of the most common opportunistic infections they experience. The prevalence of HIV infection among patients in TB clinical settings is high, up to 80 percent in some countries. The US President’s Emergency Plan for AIDS Relief (PEPFAR)<sup>9</sup> is leading a unified US Government (USG) global response to fully integrate HIV prevention, treatment, and care with TB services at the country level.

The most important work in combating TB takes place through partnerships at the country level to support national health authorities, non-governmental organizations, and community- and faith-based organizations to strengthen and implement effective TB/HIV programs.

Accelerated activities include:

- Providing HIV testing for people with TB and improving TB diagnosis for PLWHA;
- Ensuring that eligible TB patients receive HIV/AIDS prevention, treatment, and care including antiretroviral treatment, cotrimoxazole, and isoniazid to prevent active TB;
- Improving TB infection control to prevent PLWHA from

coming in direct contact with someone with active TB;

- Implementing the WHO-recommended TB treatment protocol, Directly Observed Therapy- Short Course (DOTS), in order to ensure that patients complete their TB treatment;
- To respond to the increasing rate of smear-negative and extrapulmonary TB among PLWHA, implementing laboratory-strengthening activities (eg, enhanced capacity to detect both smear negative and extrapulmonary TB among PLWHA, external quality assessment, drug resistance surveillance, and rapid detection of TB drug resistance for clinical decision-making); and
- Supporting activities to address multi-drug resistant and extensively-drug resistant TB for TB/HIV patients, including rapid TB diagnosis and treatment.

PEPFAR also supports expanding the capacity of the local health workforce to deal with TB/HIV and improving supply chain management systems for TB/HIV medications and other commodities. In addition, it is essential to establish linkages between TB treatment and antiretroviral treatment so that people who are co-infected receive the medical attention they need.

## **Koch’s Postulates Revisited**

Very soon after the announcement of the postulates 128 years ago, it became apparent that in some cases, all the conditions for proving a causative agent and its transmission could not be met.

In 1996, Fredericks and Relman summarized the problem in a landmark article in *Clinical Microbiological Reviews*:<sup>10</sup>

The critical elements of Koch’s postulates include a specific association of the microbe with the disease state; scientific concordance of microbiological, pathological, and clinical evidence; isolation of the microbe by culture on lifeless media; and reproduction of disease by inoculation of the cultured organism into a host. These stringent criteria provide a framework for thinking about the proof of microbial disease causation. For diseases like tuberculosis, these postulates have been quite successful. Koch was able to visualize *Mycobacterium tuberculosis* in diseased to reproduce the disease in animals upon inoculation from pure culture. Animals and people without disease were found not to have *M. tuberculosis* in tissues. However, even Koch was aware of the limitations imposed by these postulates. He believed that cholera and leprosy were caused by specific visible microbes, but he could not fulfill all of the postulates for disease causation. Although *Vibrio cholerae* was isolated from patients with cholera in the time of Koch, it was also isolated from healthy subjects, thereby defying the specificity of association demanded by Koch’s second postulate.

Scientists have been no more successful today than a century ago in culturing the etiologic agent of leprosy, *Mycobacterium leprae*. The inability to isolate *M. leprae* in pure culture prevents the fulfillment of Koch’s third postulate. Nonetheless, Koch stated, ‘Therefore, we are justified in stating that if only the first two conditions of the rules of proof are fulfilled, i.e., if the regular and exclusive occurrence of the parasite is demonstrated, the causal relationship between parasite and disease is validly established.’

The limitations of Koch’s postulates, evident in the 1800s, are even more pronounced today. Organisms such as *Plasmodium falciparum* and herpes simplex virus or other viruses cannot be grown alone, i.e., in cell-free culture, and hence cannot fulfill Koch’s postulates, yet they are unequivocally pathogenic. Similarly, certain microbes such as human immunodeficiency virus (HIV) exhibit a host range that is restricted to humans; they cannot produce typical disease in other hosts, thereby making impossible or unethical the final fulfillment of the third postulate.



In contrast to the beliefs of Koch and those of his era, we are well aware today that microbial pathogens often cause subclinical infection. For example, the vast majority of patients exposed to *M. tuberculosis* will simply develop a silent infection accompanied by microscopic forms of pathology, marked by the presence of a positive tuberculin skin test, and will not go on to develop active disease.<sup>10</sup>

Although Koch's postulates were of incalculable value in their first application, new knowledge has required major changes. Fredericks and Relman presented this revision in their 1996 review:

1. A nucleic acid sequence belonging to a putative pathogen should be present in most cases of an infectious disease. Microbial nucleic acids should be found preferentially in those organs or gross anatomic sites known to be diseased, and not in those organs that lack pathology.
2. Fewer, or no, copy numbers of pathogen-associated nucleic acid sequences should occur in hosts or tissues without disease.
3. With resolution of disease, the copy number of pathogen-associated nucleic acid sequences should decrease or become undetectable. With clinical relapse, the opposite should occur.
4. When sequence detection predates disease, or sequence copy number correlates with severity of disease or pathology, the sequence-disease association is more likely to be a causal relationship.
5. The nature of the microorganism inferred from the available sequence should be consistent with the known biological characteristics of that group of organisms.
6. Tissue-sequence correlates should be sought at the cellular level: efforts should be made to demonstrate specific *in situ* hybridization of microbial sequence to areas of tissue pathology and to visible microorganisms or to areas where microorganisms are presumed to be located.
7. These sequence-based forms of evidence for microbial causation should be reproducible.

In Fredericks' and Relman's summary, some of the reasons for these additions to the original postulates are that:

Many viruses do not cause illness in all infected individuals, a requirement of postulate #1. An example is poliovirus, which causes paralytic disease in about 1% of those infected. Further compromising postulate #1 is the fact that infection with the same virus may lead to markedly different diseases, while different viruses may cause the same disease. Postulates #2 and #3 cannot be fulfilled for viruses that do not replicate in cell culture, or for which a suitable animal model has not been identified.

The application of nucleic acid-based methods of microbial identification has made Koch's postulates even less applicable. Polymerase chain reaction and high-throughput sequence analyses have revealed a great deal about microbes that are associated with pathology or disease, but proving causation has become even more difficult as the number of uncultivable viruses rapidly multiplies. Nucleic acid based

detection methods are so sensitive that they detect small numbers of viruses that may occur in the absence of disease. The use of these new methods has led to revised versions of Koch's postulates that are fundamentally sound: both hepatitis C virus and human papillomaviruses were convincingly shown to be causative agents of hepatitis and cervical cancer, respectively, long before methods were developed for propagation of the viruses in cell culture.

## **Carnivorous Cows**

Complicating current revisions and additions to Koch's postulates is the unique concept of prion diseases.<sup>11</sup>

Belay et al write:

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of animal and human brain diseases that are uniformly fatal and often characterized by a long incubation period and a multifocal neuropathologic picture of neuronal loss, spongiform changes, and astrogliosis. Investigators believe the etiologic agents of TSEs are abnormal conformers of a host-encoded cellular protein known as the prion protein. Prion diseases do not characteristically elicit an immune response by the host, and the mechanism of brain damage is poorly understood. However, progressive neuronal accumulation of the disease-associated prions may damage neurons directly, and diminished availability of the normal prion protein may interfere with the presumed neuroprotective effect of the normal prion protein, contributing to the underlying neurodegenerative process.

Prion diseases attracted much attention and public concern after an outbreak of bovine spongiform encephalopathy (BSE) occurred among cattle in many European countries and scientific evidence indicated the foodborne transmission of BSE to humans. The classic form of Creutzfeldt-Jakob disease (CJD) was first reported in the 1920s, decades before the first BSE cases were identified in the mid-1980s. About 10%–15% of CJD cases occur as a familial disease associated with pathogenic mutations of the prion protein gene, and about 85% of classic CJD cases occur as a sporadic disease with no recognizable pattern of transmission. The stable, almost predictable, occurrence of the disease in many areas of the world, primarily in the elderly, led to the speculation that sporadic CJD may occur from *de novo* spontaneous generation of the self-replicating prions, presumably facilitated by somatic random mutations. Beginning in the 1970s, iatrogenic person-to-person transmission of the CJD agent was reported in a small percentage of CJD patients.

This iatrogenic spread involved the use of contaminated corneal and dura mater grafts, neurosurgical equipment, and cadaver-derived human growth hormone. At present, the number of iatrogenic CJD cases is on the decline as a result of public health preventive measures implemented as the various modes of transmission were identified.

## **Etiologic Agent of Prion Diseases**

"Most of the earliest studies done to identify the agents of TSEs focused on describing the causative agent of scrapie, a prion disease of sheep known to have been occurring in Europe for centuries. Lack of suitable laboratory models or cell culture systems had limited the efforts to characterize the scrapie agent. However, the successful transmission of scrapie to mice in 1961 greatly facilitated the identification and characterization of the scrapie agent. Several theories had been proposed to describe its characteristics. Owing to the transmissibility of the agent, retention of its infectivity after filtration, and the long incubation period before disease onset, scrapie was thought to be caused by a slow virus. The possibility that the agent could be a viroid was considered also. However, no viral particles or disease-specific nucleic acids were identified in association with scrapie infection. Resistance of the scrapie agent to radiation, nucleases, and standard sterilization and disinfection agents, and its inactivation by procedures that modify proteins led to

the suggestion that the scrapie agent is not a virus but, instead, might be composed primarily of a protein. In 1966, Alper et al. suggested the possibility that the scrapie agent could replicate in the absence of nucleic acids. Pattison & Jones also investigated this possibility and suggested that the scrapie agent might be a basic protein or associated with such a protein, thus igniting a controversy among many of their contemporaries. In 1967, Griffith carefully outlined the potential pathways by which such a protein agent could support its own replication.”

### **Generating a Prion with Bacterially Expressed Recombinant Prion Protein**

Fei Wang, Xinhe Wang, Chong-Gang Yuan, and Jiyan Ma wrote:

The prion hypothesis posits that a misfolded form of prion protein (PrP) is responsible for the infectivity of prion disease. Using recombinant murine PrP purified from *Escherichia coli*, we created a recombinant prion with the attributes of the pathogenic PrP isoform: aggregated, protease-resistant, and self-perpetuating. After intracerebral injection of the recombinant prion, wild-type mice developed neurological signs in ~130 days and reached the terminal stage of disease in ~150 days. Characterization of diseased mice revealed classic neuropathology of prion disease, the presence of protease-resistant PrP, and the capability of serially transmitting the disease; these findings confirmed that the mice succumbed to prion disease. Thus, as postulated by the prion hypothesis, the infectivity in mammalian prion disease results from an altered conformation of PrP.<sup>12</sup>

Prions are specific proteins found mainly in the nervous system, where – in their normal forms – they may have important functions. For example, studies on sea slugs, *Aplysia*, suggest that prions have a crucial role in memory formation (Kausik et al., 2010)<sup>13</sup> Infectious prions are abnormal (aberrant) forms of prion proteins that replicate inside the host by forcing normal proteins of the same type to adopt the aberrant structure. This has a domino effect whereby a small number of aberrant prions can affect many normal ones and eventually lead to disease. As the aberrant prions form amyloids — aggregates of protein — in the cells, the cells die, creating holes in the brain.

Prions are the only known case of self-propagating pathogenic proteins, and they are able to cause severe illness even though they seem to be just protein molecules. Unlike bacteria, viruses or other known pathogens, they have no information encoded in nucleic acids (DNA or RNA) about how to invade and replicate within the host. There is still a veil of mystery around prions and exactly how they replicate, cross the blood-brain barrier, and cross the species barrier (ie, infect different species of host).

It was in the 1960s that investigators first found that TSE disease-causing agents appeared to lack nucleic acids. Tikvah Alper suggested that the agent was a protein. This idea sounded heretical because all other known disease-causing agents contained nucleic acids and their virulence and pathogenesis were genetically determined.

To prove that a TSE is caused by prion protein, purified aberrant prions must be used to transmit the disease. In February 2010 this was done, adding further evidence for the protein only hypothesis.<sup>12</sup>

### **Control of Bovine Spongiform Encephalopathy (BSE)**

*BSE was first recognized in the United Kingdom in 1986, where it caused a large outbreak among cattle. The leading hypothesis for the origin of BSE is cross-species transmission of scrapie to cattle via the feeding of meat and bone meal that was contaminated by the inclusion of scrapie-infected sheep parts. Spontaneous occurrence of the disease in cattle, much like sporadic CJD in humans, has also been*

*hypothesized. Although the origin of BSE remains controversial, it is widely accepted that the practice of using rendered BSE-infected carcasses for cattle feed had amplified the outbreak until a ruminant feed ban was instituted in 1988. Because of concerns about cross-contamination of cattle feed with prohibited material intended for other species, a specified bovine offal ban (also known as specified risk material ban) was introduced in 1990 to remove the known infectious parts of cattle from all animal feed. Although a dramatic decline in the BSE outbreak was registered in response to this feeding ban, over two million potentially infected cattle were butchered and consumed in the United Kingdom. Some risk of human disease remains since as little as ten mg. of infected material has been shown to be infectious in experimental animals.<sup>11</sup>*

### **Conclusions: Optimal Use of Public Health Resources**

Koch’s postulates, useful as they were when announced in 1882, have had a rough ride intellectually, both at their inception and in their application to the many diseases to which they were applied. After millennia of ignorance, superstition, and abject fear of tuberculosis as inevitable, Koch’s sudden explanation and proof of bacterial transmission brought strict patient isolation. Unrelated social changes were occurring at the time, with widespread improvement in housing, crowding, sanitation, and nutrition, all of which were important in subduing the disease. Much later, the most critical development of all, the antibiotics, produced a further remarkable dip in TB mortality—offset since 1985 by the current surge of AIDS/TB and highly resistant TB strains. There are still about five thousand deaths a day worldwide from TB, largely related to associated AIDS infection.

In some countries, while control of TB/AIDS by technological barriers to disease transmission such as viricidal jells, condom use, syringe exchange programs, and anti-HIV drug regimes have been useful, superstition, family structure, sexual practices, and chaotic economic and political forces (ie. in sub Sahara areas) all negate technical gains. War, rape, genocide, and poverty breed public health disaster.<sup>14</sup>

Rational clinical intervention needs at least some base of education and social stability in a target population. Without security, sanitation, nutrition, birth control, and other major changes in family lifestyle that control the role of women, it is unlikely that the disease patterns in developing countries will greatly improve. Even reasonably successful drugs and vaccines are of little use in a melee of apathy, genocide, rape, and starvation. In many regions, the most vicious problems are cultural and economic, and until these are realistically addressed, medical interventions offer little hope of success.

Today we know far more about the details of epidemiology, molecular biology, and pharmacology than we do about the obtuse human behavior that often prevents their clinical application. To affect world health, religious issues, social structure, political failure, and poverty demand focused attention.

Increased research support of sociobiologic studies of self-destructive populations is needed to teach us how to alter behaviors that block the application of rational health principles. Our need for understanding why people behave as they do lies not only in chaotic third world settings, but in rich nations whose populations approach a sixty percent obesity rate and a metabolic syndrome epidemic.

Informative research results analyzing public health failures would far outweigh their costs in health care expenditures and lives saved. The ultimate laboratory is the village, the town, and the metropolis.

In each, to study why people act as they do in blocking the obvious measures that would enhance their health and lives, would add enormously to human welfare.

Perhaps it is time for a Koch's Postulates equivalent to explain the crippling impedance of human behavior.

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# Breast Cancer Worry among Women Awaiting Mammography: Is It Unfounded? Does Prior Counseling Help?

Susan K. Steinemann MD, FACS; Maria B.J. Chun PhD, CHC, CPC-A; Dustin H. Huynh MD; and Katherine Loui BA

## Abstract

*The purpose of this study was to explore the prevalence of breast cancer anxiety and risk counseling in women undergoing mammography, and the association with known risk factors for cancer. Women awaiting mammography were surveyed regarding anxiety, prior breast cancer risk counseling, demographic and risk factors. Anxiety was assessed via 7-point Likert-type scale (LS). Risk was defined by Gail model or prior breast cancer. Data were analyzed by nonparametric methods; significance determined at alpha = 0.05. Of 227 women surveyed, 54 were classified "higher risk". Counseling prevalence was similar (52%) for all ethnic groups, but higher (72%,  $P < 0.001$ ) for "higher risk" women. On average, women awaiting screening/diagnostic mammography were somewhat worried (median LS = 4). Worry was significantly higher ( $P < 0.05$ ) in "higher risk" women (LS = 5), and in women living outside Honolulu (LS = 6). Counseling by primary care physicians (PCP) did not correlate with lower worry scores. It was concluded that most women awaiting mammography are not unduly anxious. Additionally, the findings showed a correlation between a woman's concern about developing cancer with known risk factors and rural residence.*

## Introduction

Recent advancements have improved our ability to assess breast cancer risk and to impact that risk by chemoprevention, aggressive surveillance, and surgery. However, the proper deployment and use of breast cancer screening is an area of much debate among physicians, and confusion among patients. In 2009, the United States Preventive Services Task Force (USPSTF) changed its recommendation to biennial, rather than annual, screening mammography for the average risk woman.<sup>1</sup> This recommendation cited potential harms of screening, including psychological distress.

Despite, or perhaps because of, an abundance of information regarding breast cancer risk, patients often inaccurately assess their risk for cancer.<sup>2</sup> Women tend to overestimate their breast cancer risk,<sup>3,4</sup> and this could be a source of significant anxiety, exacerbated by the process of mammography.<sup>5</sup> Though "nonpathological worry" about breast cancer might encourage women to engage in the protective behavior of screening mammography,<sup>6</sup> generalized inappropriate anxiety about breast cancer may result in decreased compliance with screening recommendations.<sup>7</sup> In the American Cancer Society 2010 screening guidelines for breast cancer, Smith comments, "...methods for improved communication and strategies to reduce avoidable anxiety are a priority area for applied research, and a priority area for adoption of successful strategies."<sup>8</sup>

Breast cancer risk counseling may be one way to impact cancer "worry" by imparting a more accurate perception of breast cancer risk.<sup>3</sup> Ostensibly, breast cancer risk counseling could be initiated by the primary care physician,<sup>7</sup> perhaps coinciding with the ordering of screening mammography. However, breast cancer risk counseling may not be routinely done. Reasons for the lack of counseling may be lack of time, lack of knowledge, or concerns about needlessly increasing patients' fear. This latter concern may be corroborated by

a study showing that, among less-educated women, breast cancer risk counseling led to reduced mammography use.<sup>9</sup>

The aim of this study was to explore breast cancer anxiety among a multiethnic population of women awaiting mammography. The study sought to determine the prevalence and degree of worry about breast cancer, and the association of worry with demographic factors, and with known risk factors for developing breast cancer. Additionally, there was an attempt to determine the prevalence of breast cancer risk counseling, the likelihood of counseling among different ethnic groups and breast cancer risk groups, and to evaluate for any evidence of the impact of prior counseling on breast cancer worry.

## Methods

This prospective, observational study was conducted over four months (August-November 2006) at the university-affiliated Queen's Medical Center Women's Health Center. A convenience sample of women scheduled for mammography were surveyed immediately prior to their mammogram. Informed consent was obtained from all women. The study was approved by the Queen's Medical Center Research and Institutional Review Committee. The study's findings and conclusions do not necessarily represent the views of Queen's Medical Center, Honolulu, Hawai'i.

Women awaiting mammography in the reception area of the Women's Health Center were asked to complete a 9-item survey with questions on ethnicity, concern about developing breast cancer, prior breast cancer risk counseling, and current desire for breast health counseling. Additional historical data relevant to breast cancer risk was provided by a questionnaire completed by the patients and imaging technologists. Anxiety was assessed via 7-point Likert-type scale (LS): "1" indicating "not at all worried", "4" indicating "somewhat" and "7" indicating "extremely worried." "Higher risk" women were defined as those with a prior history of breast cancer, or a Gail model<sup>8</sup> predicted 5-year cancer incidence of  $>2\%$  and  $>1.5$  times risk for age.

A biostatistician analyzed data using nonparametric statistics (Kruskal Wallis and Wilcoxon-Mann-Whitney tests.) Significance was determined at alpha = .05 with 2-tailed tests.

## Results

The 227 women surveyed represented 6% of the approximately 4,000 women undergoing mammography at the institution during that time. Response rate was over 90%; there was no noticeable difference in ethnicity between responders and non-responders. Ethnicity of responders was as follows: 14% Hawaiian/Pacific Islanders, 63% Asian, 17% Caucasian, 6% other, 98% of women lived on O'ahu, 70% of these in Honolulu, 96% reported having a primary care physician, 54 women (24%) were classified "higher risk" by Gail model or a prior history of breast cancer.

Fifty-two percent of women reported having been counseled by a physician regarding their breast cancer risk. Counseling prevalence did not differ by age, residence, or ethnicity. "Higher risk" women were more likely to have received counseling prior to mammography (72%,  $P < 0.001$ ).

On average, women awaiting screening or diagnostic mammography were somewhat worried about developing breast cancer (mean LS = 4.1, median LS = 4). Worry was significantly higher in "higher risk" women (median LS = 5,  $P < 0.05$ ). Women who had traveled to Honolulu for their imaging were also significantly more worried than those who lived in the city (median LS = 6,  $P < 0.05$ ). We noted a non-significant trend toward increased worry (median LS = 5) in obese women ( $P = 0.06$ ), smokers ( $P = 0.1$ ), and Asian, Hawaiian and Pacific islanders ( $P = 0.06$ ). Counseling by a primary care physician did not correlate with lower worry scores, but there was a trend toward lower worry scores (mean LS = 3.5, NS) in those few counseled by a medical oncologist.

## Discussion

The population of women having mammography at this institution parallels the population of the state in its ethnic diversity. Almost all of the women having mammography maintain contact with a primary care physician. Though almost half of women stated they had not received counseling about their breast cancer risk, there did not appear to be any racial disparity in the prevalence of counseling. Counseling had been appropriately provided more frequently to higher risk women. The fact that counseling by a primary care physician did not appear to correlate with lower worry scores may be related to the subset of women who received counseling. We do not have information on the level of worry of women before they were counseled, but because they were at higher risk and/or may have requested information about breast cancer, one could reasonably hypothesize that their baseline cancer worry was higher, and that counseling reduced their worry to the level of women who had not requested or received information about their breast cancer risk. Additionally, we do not have information regarding the specific aspects of the cancer risk counseling or the woman's understanding of the information provided. Women were asked broadly if they had "ever discussed their breast cancer risk with a doctor," and it is acknowledged that there is likely to be significant variation among providers of this information. The potential for greater impact from counseling (eg, by providing standardized information in multiple formats, and assessing the woman's comprehension) exists and may be a topic for future research.

The population of women in this sample appears to have a level of breast cancer worry that is commensurate with their risk factors for developing cancer. This reached statistical significance when taking into account the most commonly used risk predictor, the Gail model. However, women with minor risk factors, including those lifestyle factors (obesity and smoking) that can be modified, also tended to harbor more breast cancer worry.

Women residing in more rural areas had a similar prevalence of counseling, yet were more worried than women living inside our city. This could potentially be due to the number of women choosing to travel to this breast imaging center because of worry and/or perceived increased risk of developing breast cancer. The observation that women from rural areas harbor more worry has supported the

policy of providing same-day mammogram interpretation for women traveling from neighbor islands to the breast imaging center.

In summary, in the population of women in this study undergoing mammography, breast cancer worry was not sufficiently severe to advocate limitation of this screening modality. Theoretically, these women's concern might produce the beneficial effect of encouraging compliance with cancer risk reduction and cancer screening strategies. Women at higher risk for developing breast cancer harbor more anxiety, and thus should be targeted for efforts to reduce cancer worry.

The observational and relational data provided by this study may serve as the background for future research on the effect of breast cancer risk counseling on women's anxiety and their perception of their cancer risk, participation in breast cancer prevention protocols, and in compliance with breast cancer screening recommendations.

*The conclusions of this study do not necessarily reflect the views of the Queen's Medical Center, Honolulu, Hawai'i.*

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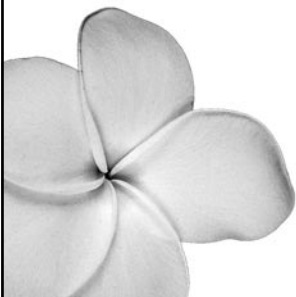
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## Training the Next Generation of Minority Health Scientists: A STEP-UP in the Right Direction

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### Introduction

In 2009, Salefu Tuvalu, a high school senior from the tight-knit community of American Samoa, traveled to Honolulu to begin an eight-week summer research internship at the University of Hawai'i John A. Burns School of Medicine. For Salefu, this was a big step into the unknown. She was one of 75 interns selected nationwide to enroll in the NIH/NIDDK STEP-UP (National Institutes of Health/National Institute of Diabetes, Digestive, and Kidney Diseases/Short Term Education Program for Underrepresented Persons) Program (<http://stepup.niddk.nih.gov>). In that year, two American Samoa students received their research training in laboratories at the John A. Burns School of Medicine, JABSOM ([http://209.18.84.241/stories/nih\\_stepup.php](http://209.18.84.241/stories/nih_stepup.php)). That summer, Salefu presented her research on the molecular pathogenesis of West Nile Virus at NIH in Washington, DC. The following year, she spent the summer at the NIDDK laboratory in Phoenix, AZ, to investigate the genetics of diabetes in American Indian communities. These experiences were transformative, with an enormous boost of self-confidence. Salefu's goal is to be the first American Samoan scientist at NIH. For her, this was a complete change in perspective and outlook. Just two years ago Salefu had questioned that a nationally run program such as STEP-UP is really intended to benefit students like herself in the remote corners of the Pacific.

In 2010, three high school students from Hana, Maui and from Moloka'i, all of Native Hawaiian descent, followed the same path to JABSOM. They were not the first STEP-UP students from Hawai'i. Since 2005, students from each of the Hawaiian Islands spent their summers at JABSOM, with all their travel and living expenses sponsored by STEP-UP. During the 2011 summer, ten high school students each from Hawai'i, American Samoa, and Guam, together with seven students from the Commonwealth of the Northern Mariana Islands (CNMI), will be research interns under the STEP-UP Program directed by UH JABSOM. Eyes are now set on enrolling students in the program in 2012 from the remaining Pacific communities associated with the United States (ie, The Freely Associated States of Micronesia (FSM), the Republic of Palau, and the Marshall Islands). With these communities coming online, the STEP-UP Program will cover the entire US affiliated communities in the Pacific. These island communities span a geographical area equivalent to the entire continental US.

### The STEP-UP Program

Annually, STEP-UP selects from throughout the nation, 75 students from approximately 300 qualified applications to be trained in research laboratories over an 8-week period. Stipends and travel expenses are provided. The typical STEP-UP intern is 16 to 18 year old, who has very little knowledge of what a career in medical

research entails, other than perhaps those portrayed in television series in episodes such as the CSI. The common elements in their STEP-UP applications' Personal Statements are a sense of curiosity in medicine and ideas of the ways that modern medicine can make a positive difference in their families and communities. Most importantly, the youngsters see themselves becoming part of the solution, as future "doctors" finding cures for those diseases that they have known all their lives. These are the key ingredients needed to help them excel in the 8-week intensive research internship. With little basic science knowledge, the students typically face a steep learning curve. Ironically, the big hurdle for them is usually not the amount of subject matter materials and laboratory techniques that they have to master but the feeling of intimidation as they are transplanted from the comforts of home and classrooms into research facilities crammed with a jungle of laboratory equipment. Much patience is demanded from the interns' research mentors who are University and JABSOM faculty members accustomed to the fast-paced and sophisticated research in an academic environment. These mentors are all volunteers for the STEP-UP program. They donate their precious time and efforts to coach these young interns through every step of scientific investigations. The mentors' challenge is to teach cutting-edge research at a level that a high school student can comprehend.

At NIH, Washington, DC, STEP-UP interns from the many parts of the nation meet each year to present their research projects. Senior NIH staff scientists have often commented that the level of maturity and sophistication demonstrated by the STEP-UP interns equals that of their own graduate students. They all agree that the enthusiasm radiated by these young interns in their own research projects is unmatched by anyone on NIH campus, including post-doctoral fellows.

### High School STEP-UP: Past, Present, & Future

The NIH/NIDDK STEP-UP program was launched in 1994 as the National High School Student Summer Research Apprenticeship Program. The Program was the brainchild of Dr. Lawrence Agodoa at the Office of Minority Health Research Coordination, NIDDK. The rationale for the STEP-UP stemmed from NIDDK's Strategic Plan to address health disparity among minority and disadvantaged populations in the US that bear a disproportionate burden of major severe and costly diseases (<http://www.healthypeople.gov/2020/about/disparitiesAbout.aspx>) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497467/pdf/12500958.pdf>). It was recognized that to address health disparities, a workforce of health professionals and researchers who are culturally competent and sensitive to the needs of the minority and disadvantaged community is vital to success (Strategy II.C in <http://minorityhealth.hhs.gov/npa/files/>

Plans/HHS/HHS\_Plan\_complete.pdf). It was believed that the most efficient and effective means to alleviate health disparity would be to produce or expand the healthcare workforce within the affected populations/communities. The strategy then was to establish a pipeline of such individuals with career goals in healthcare and medical research, and provide them with the necessary support and tools to succeed. There is no argument that such pipelines should extend from the earliest possible age groups and continue beyond post-graduate education. STEP-UP's mission is to perform outreach and provide biomedical research experience to targeted populations at the earliest possible, and logistically feasible, educational levels. High school students over the age of 16 would "fit the bill." Since its inception, STEP-UP has recruited close to one thousand high school students (11th and 12th graders) nationwide and has given each student a hands-on research internship experience under the tutelage and mentorship of a research scientist. A recent survey of STEP-UP graduates from the past four years revealed that the majority (>90%) pursued a biomedical science degree in college. A longer follow-up period will be necessary to determine if they will eventually be part of the healthcare and research professional workforce upon graduation.

The NIDDK STEP-UP has not gone unnoticed within NIH. In the past year, several initiatives similar to STEP-UP were issued as Requests for Applications (RFAs) by other Institutes and Centers (ICs) within NIH. For example, the National Institute of Allergy and Infectious Diseases (NIAID) Science Education Awards (<http://grants.nih.gov/grants/guide/pa-files/PAR-11-086.html>) and the National Institute on Minority Health and Health Disparities (NIMHD) Science Education Initiatives ([http://www.nimhd.nih.gov/hdss/nimhd\\_SE\\_initiative.html](http://www.nimhd.nih.gov/hdss/nimhd_SE_initiative.html)) were launched to support research training at the high school level. The training programs that these new initiatives support are locally focused and do not establish a national network/program. Only some of these initiatives have a focus on minority populations. Nevertheless, they will significantly contribute to expand the pool of young students suitable to contribute to the pipeline of medical researchers.

### **Plans for the Pacific**

Prior to 2009, the furthest geographical reach of the STEP-UP program in the Pacific was Hawai'i. Most STEP-UP interns were from the continental US. The US-affiliated communities of American Samoa, Guam, the Commonwealth of Northern Mariana Islands (CNMI), Federated States of Micronesia (FSM), the Republic of Palau, and the Marshall Islands did not participate. This omission may have stemmed from the sheer physical distance and isolation of these small islands from Washington, DC, compounded by the often sparse and disruptive nature of electronic communications. Timing was just right when the oversight was noted by Senator Daniel K Inouye and brought to the attention of Dr. Agodoa and the Institute Director of NIDDK, Dr. Griffin Rodgers, as Congress and President Obama issued the America Recovery and Reinvestment Act (ARRA). ARRA funds were released to JABSOM to support STEP-UP activities that would cover the entire Pacific region.

Potentially facing similar logistical challenges, the JABSOM directed Pacific STEP-UP project launched its activities in American Samoa. This was possible because the initial steps were facilitated by JABSOM's AHEC (Allied Health Education Centers) which had established groundwork in high schools to raise awareness and interests in health related careers. Guam and CNMI soon followed as STEP-UP gained credibility. At each locale, STEP-UP sought collaborations from local colleges, Departments of Education, and Departments of Health. These groups were encouraged to form partnerships, participate, and support research training. This approach has been a key factor in the receptiveness and success of STEP-UP because it promotes a sense of ownership and responsibility in line with the core mission. Completing the Pacific STEP-UP network will be the Freely Associated States of Micronesia (FSM). Historically, JABSOM has had a strong presence here, with the establishment of the Pacific Island Health Officers Association (PIHOA) in the 1960s. With the help of Dr. Gregory Dever from PIHOA, STEP-UP has been enthusiastically welcomed by island health administrators and educators.

For these and most island communities, an alternate approach is being tried. Because of the scarcity of biomedical research infrastructures and budget constraints that prohibit bringing all students to JABSOM to receive training, research training laboratories are being established at the local community colleges. The plan is to enable local faculty mentors to adopt and incorporate molecular techniques in their STEP-UP interns' research projects. Much of the needed research equipment is being donated from NIH's surplus equipment warehouse. It is envisioned that this resource will be available to support future equipment needs for STEP-UP training. Workshops are being conducted by JABSOM faculty and staff at the local colleges to familiarize potential STEP-UP mentors with lab equipment operations and the proper research techniques. With appropriate and adequate support from the local government, it is envisioned that these research-training facilities will become self-sustaining.

### **Conclusion**

With its modest budget of just under \$170,000/year to support a handful of students from each Pacific region, one could argue that STEP-UP in the Pacific may be seen as just a symbolic gesture. But on another measure, if STEP-UP can ignite a spark in the life of just one Pacific Islander like Salefu Tuvalu by opening the door to the many possibilities of medical sciences and research, and in doing so win over the support of the local government for STEP-UP's missions, it may just be the nucleus needed to grow the next generation of medical scientists.

### **Acknowledgements**

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## ❖ COLE PORTER WAS RIGHT! SMOKE GETS IN YOUR EYES.

As if there were not enough powerful reasons why a person should quit using tobacco, a study in the journal *Ophthalmology* established a link in all types of uveitis. Associate Professor Nisha Acharya MD and a team at the University of California San Francisco, examined 564 smokers over a 7-year period from 2002 to 2009, and compared them with 564 randomly selected patients. Their primary finding was that smokers were 2.2 times more likely to have ocular inflammation than people who had never smoked. Not only was it found that evil weed is associated with all types of uveitis, but Phoebe Lin MD, PhD at Duke University, noted that the ratios for smoking and uveitis are equal to or higher than the associations between smoking and macular degeneration. Tobacco serves up a double-barreled blast threatening eyesight.

## ❖ TRIM YOUR BIG BELLY, BUT TOLERATE YOUR BIG BEHIND.

The Mayo Clinic's latest disease report, published in the *Journal of the American College of Cardiology*, offers more information about good fat and bad fat. Data were pooled from 16,000 patients with heart disease who had suffered a heart attack or had a major heart procedure. The new report repeats that obesity is clearly an important factor, but it's mostly about fat distribution and not total fatness. Patients with bulging waistlines, by comparing waist to hip measurements, had a higher risk of death. Men with waists of 40 inches or more and women with 35 inches or more were 1.7 times as likely to die during the follow-up period as those with normal waists. The report suggests that people can be overweight without raising the danger of heart attack if the pounds are carried on the thighs and hips.

## ❖ A DOCTOR IS A DOCTOR EVEN WHEN HE'S A DEFENDANT.

In Jonesboro, Arkansas, Dr. Stephen Eichert was being sued for malpractice. The plaintiff claimed that Dr. Eichert had failed to conduct appropriate pre-operative tests and had failed to explain the surgical risks. She wanted \$75,000 for the cost of the two operations and follow-up visits, and reimbursement for lost wages. In addition she expected an amount for pain, suffering and mental and emotional anguish. As the attorneys were delivering opening statements, one of the jurors became ill. Dr. Eichert promptly provided appropriate care for the ailing juror in front of the jury. The juror's name and specific condition were not disclosed. The attorney for the plaintiff promptly asked for a mistrial, and Dr. Eichert's attorney agreed.

## ❖ A NEW CHAPTER FOR THE VAGINA MONOLOGUES.

At Johns Hopkins Medical Center, a surgical transplant team successfully removed a healthy donor kidney through the vagina. Similar operations have been performed for cancer or a failing kidney, but this is the first time a healthy kidney was removed for donation. The kidney was successfully placed in the abdomen of the donor's niece, and both are doing well. Dr Robert Montgomery, chief of transplant surgery, said that removing the tissue through a natural opening provides for a faster recovery and better cosmetic result.

## ❖ THE DIFFERENCE BETWEEN A PHARMACEUTICAL COMPANY AND A TERRORIST IS THAT YOU CAN DEAL WITH A TERRORIST.

Bristol-Myers has manufactured a drug shown to extend survival of patients with late stage melanoma. In a trial of 676 melanoma patients, those treated with Yervoy (ipilimumab) lived 10 months, on average, compared to six months for a cohort not taking the drug. Other patients taking the drug were also more likely to be alive after two years. Yervoy is a monoclonal antibody which boosts the body's immune system's ability to fight tumors. Biotech drugs are costly to develop, but they are difficult to copy and give drug makers less fear of generic competition. To no one's surprise, there is a substantial price tag. Bristol will sell the drug for \$30,000 per infusion and a recommended four dose treatment course will cost \$120,000. So, patients with terminal melanoma might extend their lives for four months at a cost of \$1,000 per day.

## ❖ FAT AMERICA PART I: MORE BAD NEWS.

Reporting in the *American Journal of Preventive Medicine*, a research team from the Centers for Disease Control and Prevention (CDC) mapped out a diabetes belt stretching across the Deep South and Appalachia. In a county by county analysis, the team found the high-diabetes pockets touch North Carolina, Virginia, Florida, Texas, Arkansas and Oklahoma. Not surpris-

ingly, the map considerably overlays the "stroke belt" since the conditions have similar risk factors. Obesity, a sedentary lifestyle and the proportion of the population that is African-American are all higher than average in this belt. The CDC hopes that mapping these health problems will assist public health officials to target communities with preventative measures.

## ❖ FAT AMERICA PART II: A LITTLE GOOD NEWS.

In Portland, Maine, a program called "Let's Go" was established to rally schools and other sites to fight obesity in children and adults. Victoria Rogers, a pediatrician, founder and director of Let's Go, began the struggle in 2004 when she became alarmed at the number of children popping growth curves. Rather than giving lectures or brochures, she adopted a simple numerical plan. Families were urged to adopt a 5-2-1-0 routine each day: five servings of fruits and vegetables, two hours or less of screen time, one hour of exercise and zero sugary drinks. A group of health care experts and local businesses invested about \$3.7 million five years ago to help in the battle. Let's Go has expanded to more than 345 schools, many child-care centers, and after-school programs across Maine. Communities and medical practices in other states have adopted it. Southern Maine saw the obesity rate drop by 1.5%, not a huge change, but certainly a positive step. With the intent of establishing a similar road map, the CDC recently awarded 39 US communities \$257 million to make environmental and policy changes to impact behavior.

## ❖ FORGET BIG BROTHER. THINK STEVE JOBS!

If you have an I-phone in your pocket, Apple could be recording your location. That's the claim of two researchers, Pete Warden and Alasdair Allan, who published a description of their findings on line at O'Reilly Radar. They state that the Apple i-Phone and i-Pad record the devices' geographic location and time in a hidden file. The data collection began when Apple released its iOS4 mobile operating system. "It's clearly intentional, as the data base is being restored across back-ups, and even device migrations." Because the files are unencrypted and unprotected, these data have glaring privacy and security implications. They can be transferred to any machine synced with this communication marvel. If you carry one a savvy investigator can follow your every movement. ABC news asked Apple for an interview, but received no reply.

## ❖ THERE IS ALMOST NOTHING YOU CAN'T BE PUT IN JAIL FOR NOW.

The Chena River flows through Fairbanks, Alaska, and river ice was breaking up with the spring thaw. An 18 year-old high school student was jumping on the ice with friends when a 10 by 15 foot chunk broke away. He jumped on the ice floe and headed downstream. His friends tossed him a milk crate to sit on and a cooler lid for a paddle. He cruised through downtown Fairbanks before the ice got hung up and firefighters launched a boat to come to his assistance. When he got to shore he was handcuffed, taken to jail and charged with disorderly conduct for creating a hazardous condition for the rescuers. He was sentenced to 50 hours of community service and fined more than \$100. Geez, you just can't have any fun any more.

## ❖ NO OMELET FOR ME, THANK YOU. A BOILED EGG IS HARD TO BEAT.

The long-standing culinary springtime tradition of eating urine-soaked eggs continues in Dyongyang, China. According to a CNN report, pre-pubescent males collectively donate their urine at schools. The eggs are boiled in the urine according to a recipe and sold at the local market for 23 cents each. Many residents consider such dining gross, but others enjoy the eggs and say they represent the joyous smell of spring. Anyone who thinks that urine vapor is the aroma of spring has never helped put out a campfire.

## ADDENDA

❖ Based on the average number of alcoholic drinks consumed per person, the booziest town in the United States is Austin, Texas. First runner-up is Milwaukee with Providence, R.I. San Francisco and Chicago rounding out the top five. Honolulu did not appear on the list.

❖ Bananas were virtually unknown in America until 1876 when they were offered at the Philadelphia Centennial Exposition for ten cents each.

❖ Most popular rock song in history: "You've Lost That Lovin' Feeling."

❖ Eighty-seven condoms are used each second on Valentine's Day in the United States.

❖ Running over a mongoose at 65 mph is not considered fast food.

ALOHA AND KEEP THE FAITH **rt** ■ *(Editorial comment is strictly that of the writer.)*

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