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LETTERS TO THE MJM

AMERICAN COLLEGE OF PHYSICIANS, INTERNAL MEDICINE CONFERENCE 2010

Imagine thousands of physicians under one roof, on a three day mission to strengthen their clinical knowledge with the latest guidelines. Each year, the American College of Physicians organizes a meeting to update internal medicine physicians, fellows, residents and medical students on the most current data available on the pathogenesis, diagnosis, and treatment on everything from congestive heart failure to eosinopilic esophagitis. Perhaps even more impressive, this conference offers free registration to all student members. This year, the event took place at the Metro Toronto Convention Centre (April 22-24, 2010) and, for the first time, was held outside of the United States (http://www.acponline.org/meetings/internal_medicine/2010/).

The American College of Physicians (ACP) is, with a membership of 129,000 people, the largest international organization of internists which includes internists, internal medicine subspecialists, fellows, residents, and medical students. One of the College's missions is education, and the annual Internal Medicine conferences are an excellent example of this commitment. The meeting is structured to appeal to all participants, with seminar tracts focusing on each subspecialty of internal medicine as well as ObGyn, Neurology, Community Medicine, and Psychiatry. As such, it is a great opportunity for early trainees and medical students to obtain high-quality, concise information about the latest trends in health care. In addition to providing seminar sessions, hands-on clinical skills demonstrations, and opportunities to present research, the meeting is a good way to network with colleagues and leading physicians throughout the United States and Canada during the multiple social events organized at the culmination of daily academic activities.

This year's conference opened with a keynote address by Dr. James Orbinski, former president of Medecins Sans Frontieres and recipient of the 1999 Nobel Peace Prize on their behalf. Dr. Orbinski is one of the world's leading scholars dedicated to global health policy, improving access to health care, and medical humanitarianism. His inspiring talk set an enthusiastic tone which was evident during the remainder of the conference – individuals with a vision improve the lives of others – one patient, one hospital, one country at a time. Over the three days, IM2010 offered over 250 scientific sessions taught by top-rated, internationally recognized faculty on subjects ranging from clinical updates to ethical issues, and even options for models of practice. This allowed attendees to fully tailor their experiences to their own areas of interest. In addition, the conference featured student and resident abstract, poster and clinical vignette competitions. Students could also take advantage of sessions on thriving during clerkship, mastering the match and student-physician mentorship forums.

Perhaps most appealing to students early in their training was the impressively equipped Herbert S. Waxman Clinical Skills Center. This area featured small group sessions (with fewer than 15 learners) on numerous procedures including ultrasound-guided central line placement, intra-articular injections, airway management, incision and drainage and many other techniques. The center also featured physical exam skills development through an audio tour of cardiac murmurs, a fundoscopy training area and a mock OSCE track in which participants are mailed written feedback by experienced standardized patient-evaluators.

Lastly, the Internal Medicine conference features 'Doctor's Dilemma', a Jeopardy-style competition, billed as the 'World Series' of medicine. This exciting game pitted teams of top residents from across the world against one another in a test of clinical knowledge from all areas of medicine.

Students interested in attending next year's conference are encouraged to visit the American College of Physicians' website and enroll as student members (http://www.acponline.org/membership/join/). In addition to free registration to Internal Medicine 2011, (April 7 – 9, 2011 in San Diego, California!), student members can take advantage of numerous benefits including clerkship preparation materials, physician mentors and free access to ACP publications. Students interested in becoming ACP student representatives are encouraged to request additional information via e-mail (abhijat.kitchlu@gmail.com).

Sincerely,
Abhijat Kitchlu

LETTERS TO THE MJM

REPERFUSION FOR STEMI IN CURRENT CANADIAN PRACTICE: ARE WE CLOSING THE CARE GAP?

INTRODUCTION

The current standard of care for patients presenting with acute ST-segment Elevation Myocardial Infarction (STEMI) includes early reperfusion therapy with either fibrinolytics or primary percutaneous coronary intervention (primary PCI). Previous registry data has shown that 30% of patients with STEMI receive neither form of reperfusion (1,2,3). Furthermore, untreated patients have 30-day mortality rates that are 2-3 times higher than those who are treated (3,4). The goal of the present study is to document the current prevalence of reperfusion therapy at three Canadian teaching hospitals and to identify underlying demographic and clinical factors that correlate with rates of reperfusion in these patients.

METHODS

Patients were identified from a prospectively collected database of all STEMI patients presenting to three teaching hospitals in Hamilton, Ontario, between April 2004 and July 2006. This institutional database contains clinical, angiographic, and outcome variables collected by individuals using standardized criteria. One of the three hospitals is equipped with cardiac catheterization facilities. Patients presenting to the other two sites had to be transferred if cardiac catheterization was required.

Thirteen clinical and demographic variables were compared in order to identify predictors of not receiving reperfusion. Variables were selected based on both their proven significance in previous studies (age, sex, time from symptom onset to presentation, history of congestive heart failure, and history of diabetes) and the possibility that they might be specifically clinically relevant (history of hypertension, stroke, peripheral vascular disease, coronary artery disease, myocardial infarction, previous angioplasty, coronary artery bypass surgery and presentation during regular working hours). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each of the variables. Multiple logistic regression using a forward selection model was used to identify independent predictors of not receiving reperfusion. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). In patients who did not receive reperfusion, a retrospective chart review was done to identify any and all reasons that treatment was withheld. Each chart was reviewed by two of the authors (M.K. and D.Y.) and any differences were resolved by consensus.

RESULTS

Data was collected on 538 consecutive patients. Of these, 272 (50%) were treated with primary PCI, 116 (22%) with fibrinolytics, 84 (16%) with fibrinolytics and rescue PCI, and 66 (12%) received no reperfusion. Although the use of primary PCI was higher at the PCI-capable hospital, the overall rate of reperfusion (i.e. primary PCI + fibrinolytic use) was not significantly different between the three sites (data not shown). Of the thirteen variables studied, we identified five that were significant predictors of not receiving reperfusion (Figure 1): onset of symptoms to emergency room (ER) arrival > 12 hours (OR 6.5, 95% CI 3.7-11.5), age > 75 (OR 5.7, 95% CI 3.3-9.7), history of congestive heart failure (OR 4.5, 95% CI 2.1-9.9), female sex (OR 2.5, 95% CI 1.5-4.2) and diabetes (OR 1.8, 95% CI 1.0-3.3). When all thirteen variables were entered into a multivariate analysis, only two were found to be significant: onset of symptoms to ER arrival > 12 hours (OR 5.1, 95% CI 2.8-9.4) and age > 75 (OR 1.08, 95% CI 1.05-1.10). The only variable found to

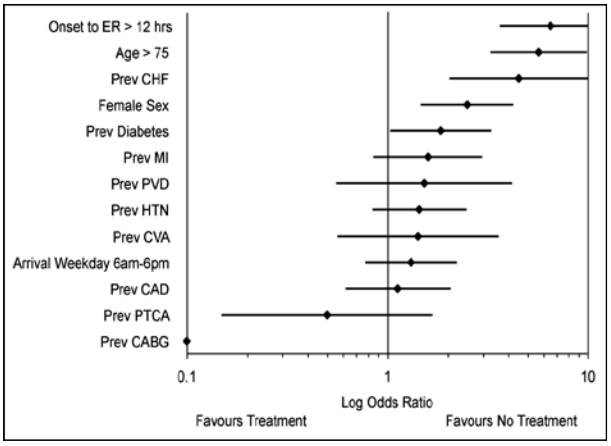

Figure 1: Forest plot of the thirteen clinical and demographic variables studied. Each point estimate represents the odds that a patient with that variable was not given reperfusion therapy. Error bars represent 95% confidence intervals around the odds ratios. ER = emergency room, CHF = congestive heart failure, MI = myocardial infarction, PVD = peripheral vascular disease, HTN = hypertension, CVA = cerebrovascular accident (stroke), CAD = coronary artery disease, PTCA = percutaneous coronary angioplasty, CABG = coronary artery bypass grafting surgery. A confidence interval could not be calculated for the variable "previous CABG" because all 18 patients with a history of CABG were treated with reperfusion.

Reason	Number of Patients	Percentage of Total
Late presentation or time of onset unclear	27	41%
Active bleeding or concern re: bleeding	13	20%
Patient or family decided on conservative management	9	14%
ECG changes resolved spontaneously before reperfusion could be offered	9	14%
Misinterpretation of ECG or delay in diagnosis of STEMI	6	10%
Physician felt that a conservative strategy was more appropriate	5	8%
Other/unknown	9	14%
	78	**118%**

Table 1: The reason(s) why reperfusion was withheld in individual patients, as identified by retrospective chart review. The numbers add to more than 100% because some patients had more than one reason identified.

favor treatment was history of previous coronary artery bypass grafting surgery (CABG), where all 18 patients with a history of CABG were treated with reperfusion. The main reasons patients were not offered reperfusion therapy were late presentation, bleeding concerns, patient preference for conservative therapy, and spontaneous resolution of ECG changes (Table 1). The unadjusted 30-day mortality of patients not treated with reperfusion was 26%, compared with 7% for those who were treated.

DISCUSSION

We found that 12% of patients presenting with STEMI did not receive primary reperfusion therapy. This represents a substantial improvement over data from several large international registries, (1,2,3) as well as over previous Canadian data (5), which showed that roughly 30% of patients are left untreated. 66% of our patients were offered early catheter-based reperfusion (primary PCI or rescue PCI), mirroring recent data from the GRACE registry (6).

Patients presenting late to the emergency department, the elderly, those with a history of CHF, women, and those with diabetes were less likely to be treated. Previous studies have shown that treatment gaps in these key subgroups have persisted over time, despite overall improvements in reperfusion rates (7). We found that two variables independently predicted no reperfusion: late presentation to the emergency department and age > 75. We know from previous studies that older age at presentation is associated with higher rates of congestive heart failure (8), perhaps explaining why CHF was not an independent predictor in our analysis. The absence of female sex as an independent predictor can be explained by the fact that women with STEMI present later to hospital and tend to be older than men (9).

Our chart review revealed that reperfusion therapy was often withheld for valid reasons (active bleeding, spontaneous resolution of ECG changes, patient preference for conservative therapy). However, the most common reason that treatment was withheld was late presentation to the emergency department. General knowledge about symptoms of acute coronary syndromes is poor (10) and large-scale efforts to educate the public are only modestly effective (11). Furthermore, many of the patients presenting late are women and the elderly, groups that often have atypical symptoms. A reperfusion rate of 88% may in fact be approaching an optimal level of reperfusion.

We found that mortality in patients not receiving reperfusion was nearly four-fold higher than in those who were given reperfusion. This demonstrates the treatment-risk paradox that exists with STEMI, where high-risk patients are least likely to be offered lifesaving therapy (12). It is possible that clinicians withhold treatment for fear of complications, even though the risk of not treating may be higher. Some have suggested that physicians should use clinical decision tools to improve the accuracy of their risk assessments (12). If reperfusion therapy is withheld because of late presentation or contraindications other than bleeding, it is important to remember that antithrombotic therapy (for example, fondaparinux) has been shown to have a mortality benefit in these patients (3,13).

The major limitation of our study is that it represents the experience of a single urban region with an organized STEMI management program and access to early reperfusion with primary or rescue PCI. It is unclear whether our experience reflects current trends in other regions of Canada. Of note, data from the GRACE registry (2) showed similar reperfusion rates in hospitals with and without PCI capabilities and also failed to show a difference in reperfusion rates between geographic regions. Conversely, an Austrian study demonstrated that reperfusion rates could be improved by reorganizing the delivery of reperfusion services in a city (4). While there has been much discussion over the last decade whether patients should receive primary PCI or thrombolysis as the initial reperfusion strategy, it is important to confirm whether all eligible patients are receiving some method of reperfusion in a timely fashion, as this has a major impact on survival. A national heart attack registry would allow us to assess rates of reperfusion across the country and identify areas for future quality improvement.

CONCLUSION

Our review of current practice patterns at three Canadian teaching hospitals found that 88% of patients with STEMI are offered acute reperfusion therapy, a substantial improvement over previous registry data. We found that patients presenting late to the emergency department, the elderly, those with a history of CHF, women, and those with diabetes were less likely to be treated. Of these, only age and late presentation were found to be independent predictors of not receiving reperfusion. Mortality among untreated patients remains very high and every effort should be made to optimize medical therapy in these patients.

Sincerely,

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CASE REPORT

Tracheal agenesis: A rare but fatal congenital anomaly

Suzan Ergun, Ted Tewfik*, Sam Daniel

ABSTRACT: In this report we describe a newborn with a rare case of Type II tracheal agenesis and bronchoesophageal fistula. Polyhydramnios and suspected esophageal atresia were identified during routine pre-natal ultrasound screening. Upon delivery, rigid bronchoscopy, esophagoscopy, and intraoperative fluoroscopy were performed, where both bronchi and the carina showed unusual horizontal orientation making it difficult to identify the fistula. However, a post mortem CT confirmed the diagnosis of an isolated Type II tracheal agenesis with bronchoesophageal fistula.

INTRODUCTION

Tracheal agenesis is a rare and lethal congenital anomaly, where a complete interruption or absence of the trachea is present. Since it was initially described in 1900, few cases have been published worldwide (1). The prevalence of tracheal agenesis is less than 1:50,000 with a male to female ratio of 2:1. In general, 52% of cases are associated with premature delivery and approximately half of the cases are associated with polyhydramnios (2).

Floyd et al. classified tracheal agenesis into three widely accepted anatomical subtypes (3). Type I is characterized by agenesis of the proximal trachea and by the presence of a distal tracheoesophageal fistula, whereas type II is defined by a complete absence of the trachea and by the presence of normal bifurcating bronchi. In type III, the two main bronchi arise independently from the esophagus (3).

Isolated Type II tracheal agenesis with fistula is rare, and up to 94% of cases are associated with other congenital abnormalities. Newborns with Type II tracheal agenesis usually present with polyhydramnios, respiratory distress, aphonia, cyanosis, and an inability to undergo endotracheal intubation. Currently, type II tracheal agenesis accounts for approximately 50-60% of all cases. At present, the etiology of type II tracheal agenesis is unknown and no significant karyotype exists (4).

In general, prenatal diagnoses can only be made via ultrasonography and the outcome is poor (5,6). This case report depicts an unusual situation where Type II tracheal agenesis with esophageal fistula was diagnosed independently of any other congenital anomalies.

CASE REPORT

Our patient was born to a 31-year-old G2P1A0 mother and a non-consanguineous father. Prenatal ultrasound at 25, 29, and 32 weeks showed polyhydramnios and suspected esophageal atresia. Amniocentesis reductions were performed three times during the pregnancy to reduce the volume of amniotic fluid. Aside from these findings, the pregnancy was without other known complications. The patient was delivered at 35 1/7 weeks gestation by caesarean section owing to fetal bradycardia and the suspected diagnosis

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of esophageal atresia. The baby made no audible cry. Its birth weight was 1850gm, indicative of intrauterine growth restriction (IUGR). Respiratory distress developed immediately following birth and attempts at intubation with a 2.5 mm endo-tracheal tube (ETT) failed due to the blockage below the vocal folds.

Examination showed a hypoxic newborn with a PO_2 of 63, with a blood pH of 6.8 and a PCO_2 of 135. Mask ventilation was also difficult, but an O_2 saturation of 95% was achieved following administration of 75% FiO_2.

Once stabilized, the perinatal patient was immediately transferred to the operating room of a tertiary pediatric medical center. A second intubation using a 2.5 mm ETT failed due to subglottic obstruction. Rigid bronchoscopy was performed and revealed a blind pouch below the vocal folds (fig.1).

Tracheostomy was attempted but was unsuccessful as no cervical trachea was palpable below the cricoid cartilage. Intraoperative fluoroscopy of the trachea also confirmed the subglottic stenosis and absence of the lower cervical and thoracic trachea. The presence of a bronchoesophageal fistula was identified with both bronchi originating from a flattened carina. The bronchi and carina exhibited unusual horizontal orientation and the carina demonstrated a straight continuous roof with no tracheal remnants (fig.2).

Based on these imaging studies, isolated Type II tracheal agenesis with bronchioesophageal fistula was diagnosed. The patient died within 5 hours of birth. A post-mortem CT scan revealed a 7 mm remnant segment of cervical trachea (with no lumen) running in the craniocaudal plane and confirmed the complete absence of the lower cervical and thoracic trachea. The carina originated from the esophagus and joined to the right and left main bronchi.

DISCUSSION

Floyd et al. defined Type II tracheal agenesis as complete absence of the trachea with the presence of normal bifurcating main bronchi (3). 94% of cases are associated with other congenital defects including congenital cardiac, genitourinary, gastro-intestinal, pulmonary, CNS, and musculoskeletal anomalies (3,6,7).

While the embryological mechanisms behind Type II tracheal agenesis remain controversial, it has been suggested that tracheal agenesis is a result of the abortion of the lung bud outgrowth and delayed formation of the bronchi and lungs via remnant primordial mesenchyme which often attaches to the esophagus (7). Also, while no significant genetic karyotype has been found to correlate with tracheal agenesis, homozygous Shh-null mutant mice show foregut defects similar to those seen in tracheal agenesis (8).

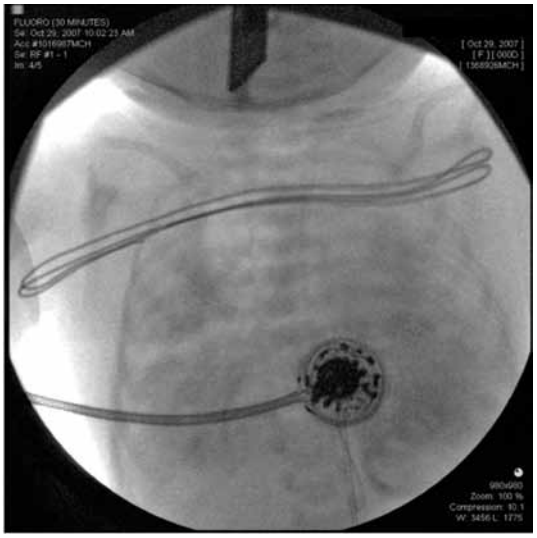

Figure 1: Notice the scope in the subglottic segment demonstrating absent cervical and thoracic trachea.

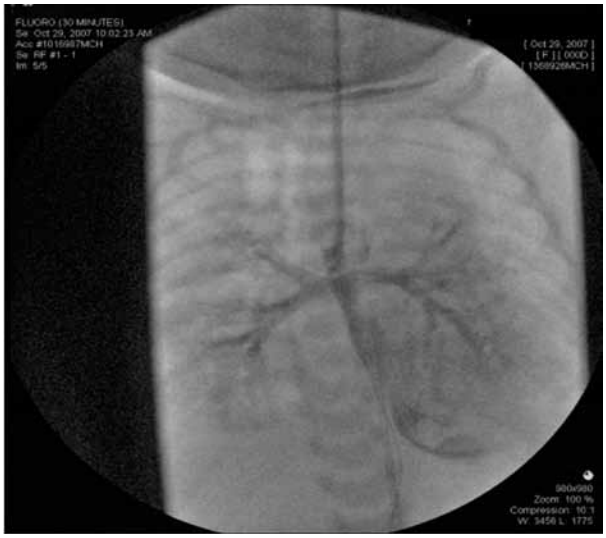

Figure 2: Note the unusual horizontal orientation of R/L main bronchi and carina (with contrast in the esophagus and bronchial tree) visualized using fluoroscopy.

Tracheal agenesis should be included in the differential diagnosis when the following clinical signs are manifested: neonate with a history of polyhydramnios, absence of an audible cry at birth, failure to intubate beyond the vocal folds, and respiratory distress (9).

In patients with tracheal agenesis, surgical correction has been proposed as a corrective measure (6). To date, only one patient with Type II tracheal agenesis has survived beyond the neonatal period. However, that surviving patient had a proximal tracheoesophageal fistula in addition to a bronchoesophageal fistula, which allowed the successful establishment of a permanent airway by performing a tracheotomy and inserting a long T tube to create a patent airway (10). While temporary management can include the insertion of an esophageal tube, depending on the extent of the fistula, infants with a complete absence of the trachea tend to die within hours of birth, as a permanent airway cannot be created. Mask ventilation can also be used to assist in temporary prolongation of life. However, there is no established medical protocol for life conservation in isolated Type II complete tracheal agenesis. Currently, this anomaly is incompatible with life and future hopes for survival will depend on surgical developments.

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CASE REPORT

Severe emphysematous cystitis: Outcome after seven days of antibiotics

Maria Sereno*, César Gómez-Raposo, Gerardo Gutiérrez-Gutiérrez, Miriam López-Gómez, Enrique Casado

ABSTRACT: We present the case of a 70-year-old woman with emphysematous cystitis. She was a diabetic patient and she was on chemotherapy treatment for a breast cancer. She complaint of severe asthenia and pain in her right lower extremity, but no fever or urinary symptoms. A computed tomography (CT) scan was suggestive of severe emphysematous cystitis. Emphysematous cystitis is a rare clinically entity, more commonly seen in diabetic, immunocompromised patients. A conservative treatment approach using antibiotics and bladder catheterization is typically successful, with a complication rate less than 20%.

KEYWORDS: emphysematous cystitis

CASE REPORT

A 70-year-old woman with diabetes diagnosed of breast cancer T1N1 several months ago treated with surgery and chemotherapy was admitted to our hospital because of severe asthenia and pain in her right lower extremity. She did not refer either urinary symptoms or fever. She was still on chemotherapy (last cycle 20 days ago). Glucose levels were not well controlled (mean over 300 mg/dl) due to corticoids use as well as chemotherapy pre-medication. More than 1 × 106 colonies of E.coli grew from her urine and blood cultures. A computed tomography (CT) scan demonstrated a thickened, trabeculated bladder wall containing pockets of gas (Figure A). These findings were suggestive of severe emphysematous cystitis (1). Intravenous Piperacillin-tazobactam was administrated with bladder catheterization (2). After one week of antibiotics, the patient improved clinically and another CT was taken, showing a considerable reduction of the gas inside bladder wall (Figure B).

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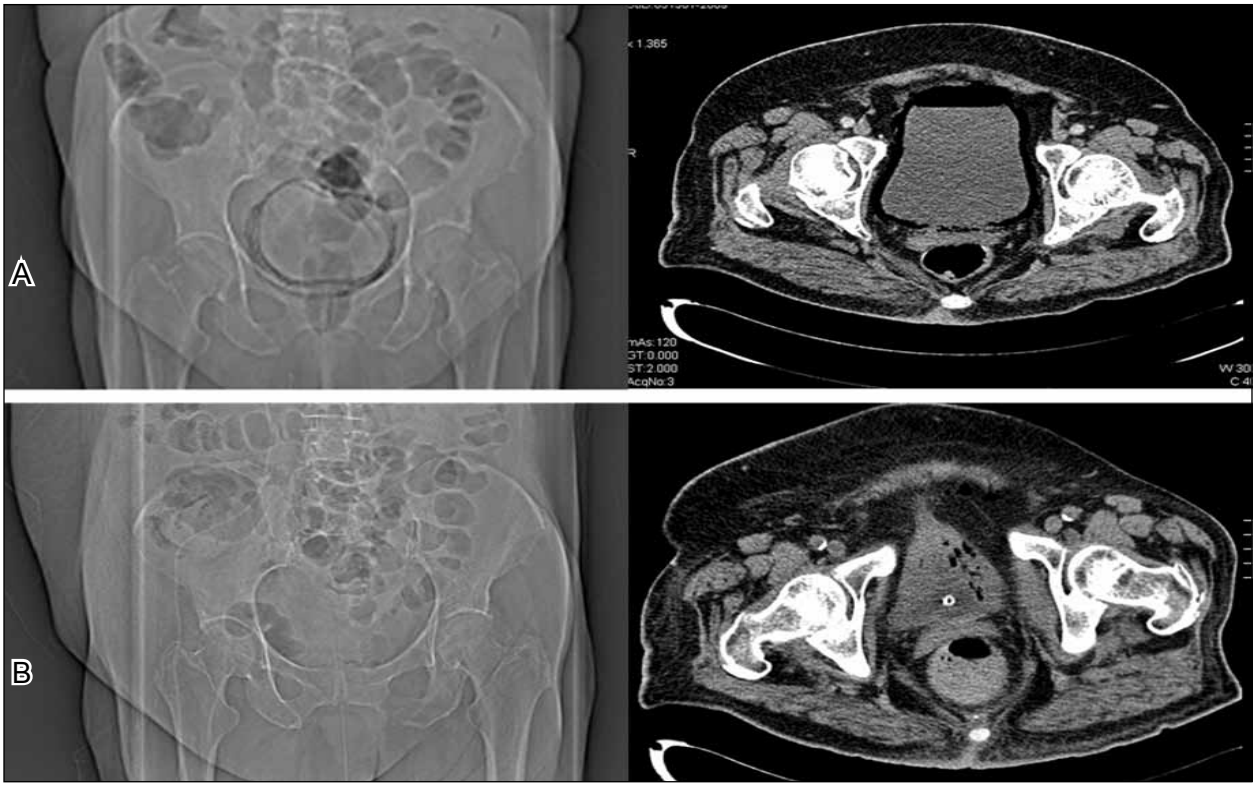
The outcome was favourable after three weeks on antibiotic treatment. So far, there is no evidence of relapse and she is on follow-up in Oncology Department

DISCUSSION

Despite belonging to a low percentage of all the urinary tract infections, gas-producing infections are relevant as they may lead to death. Three categories of this type of infections are recognized: emphymatous pyelonephritis, emphymatous pyelitis or emphymatous cystitis.

Emphymatous pyelonephritis is a necrotic infection. The gas is produced in the renal and perirenal parenchyma and 90% of the cases are reported in diabetic patients. The delay on the appropriate therapy contributes to a high mortality rate, in some case series up to 80% (3).

Emphymatous cystitis is a rare disease that is mainly diagnosed in diabetic and immunocompromised patients. It is also reported to be in association with neurogenic bladder, obstruction of the urinary tracts, catheter use and chronic infections of the urinary tract.



The microorganisms most often involved in this infection are Escherichia coli and Klebsiella pneumonia and the less common are Enterobacter, Proteus, Streptococci and Candida (4). Though, bacteria are the most common agent, fungi may also be responsible for this clinical picture (5).

The exact mechanism by which the gas is produced in the emphysematous infection is not quite clear. In diabetic patients, one of the reasons seems to be the production of CO2 by the microorganisms through the fermentation of glucose, which occurs when the glucose concentration is high. Since the emphymatous infections may occur in nondiabetic patients, it has been suggested that the urinary lactulose and tissue proteins may be useful as substrate to the gas production (6).

Another factor that may help in this process is the impaired transportation of gas due to the local inflammation or some kind of obstructive process increasing the local pressure and decreasing the circulation. This may involve tissue necrosis which becomes a good culture for pathogens to produce gas (7).

The most common clinical features are fever and abdominal pain along with dysuria, haematuria and pneumaturia (8). In our patient, the presentation was unusual with pain in her right lower extremity, but without urinary symptoms.

The diagnosis is provided by radiographic image (X-ray or CT scan). The most obvious radiographic clues are small pockets of gas in the mucous membrane of the bladder, as we can see in this picture.

Other causes for the presence of air in the bladder such as fistula with the intestine or vagina, after trauma, cancer or instrumentation, have to be excluded (3).

The appropriate treatment involves endovenous antibiotic therapy with broad-spectrum such as fluoroquinolones, penicillin with inhibitor of the beta-lactamases (imipenem, ticarcillin/clavulanate) or third-generation cefalosporins. Antifungal agents may be used (systemic or intravesical), if a fungus infection is reported (6). The full recovery from any infection with gas production depends on early diagnosis plus correction of the subjacent causes, glycemic control, long-term therapeutic with antibiotic therapy (3 to 6 weeks) and surgery, if required (3). Our patient had a fast response to intravenous antibiotic. After 7 days on treatment the radiological and clinical features had improved considerably.

The reported case shows the seriousness and the atypical presentation that this infection may assume. The diagnosis was made indeed on a diabetic patient in an unusual clinical situation. The diabetes mellitus and the poor glycemic control are

the main risk factors for this type of infection. The agent isolated from this patient, the Escherichia coli is reported as the most common. The empiric broad-spectrum antibiotic (piperacillin/tazobactam) used for the nosocomial urinary tract infection was found to be highly effective.

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CASE REPORT

A Rare Variant of a Common Nodule

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INTRODUCTION

Dermatofibromas, or benign cutaneous fibrous histiocytomas, are relatively common, slow growing, benign tumours composed of a mixture of fibroblastic and histiocytic cells. They usually manifest on the extremities (legs > arms > trunk) during early or mid adult life with a male to female ratio of 1:2 (1). In most cases, the etiology of the tumour is unknown, but is generally hypothesized to be a late histiocytic reaction to local trauma (insect bites, viral warts) or to an inflammatory condition (atopic dermatitis, lichen sclerosis, psoriasis) (1).

These lesions appear gradually over several months, may persist without change in size for years, and can regress spontaneously. They often present as asymptomatic solitary nodules, between 3 to 10mm in size, with ill defined borders that fade to normal skin. The overlying skin is red or red-brown in colour, but occasionally may appear black. The dimple sign, where a central depression within the lesion is elicited upon compression along its margin, is often conducted to aid in the diagnosis of dermatofibromata. However, it is important to keep in mind that this clinical finding is not specific for dermatofibromas, and can be elicited in various other papulonodular lesions, including blue nevi, pilar cysts, and Kaposi sarcoma (2). Because of the benign nature of this lesion, no treatment is necessary unless there is recurrent trauma irritating it (1). Excision and cryotherapy can be used in these circumstances, with cryotherapy as the preferred method due to its more cosmetically acceptable results. The recurrence rate is approximately 10% following conservative therapy, with lesions located in deep soft tissue at greatest risk of recurrence (5).

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THE CASE

A 59 year old Caucasian man presented with a 30 year history of a solitary, slowly growing tumor on his left lower leg. The referring physician had been treating him with betamethasone valerate 0.01%. The lesion had not demonstrated any bleeding, pruritus, or recent growth. The patient was otherwise in good health and denied any other symptoms. He did not recall local trauma in the area and denied a past history of any autoimmune conditions. Examination of the skin revealed a firm, well demarcated, yellowish to skin coloured plaque measuring 4.5 x 3.2 cm in diameter. Punch biopsies were taken from the center and periphery of the lesion (Figure 1).

Histologic examination revealed marked acanthosis and hyperkeratosis of the epidermis. Evident within the dermis layer was a fibrohistiocytic tumour, characterized by foamy, spindle shaped cells scattered between dense collagen bundles (Figure 2,3). The betamethasone valerate was discontinued and no other medication course was initiated. Instead, the patient was closely monitored.

DISCUSSION

Although dermatofibromas are common, the xanthomatous variant (XDF) is extremely rare (3). While other subtypes exhibit various numbers of lipid-containing tumor cells with a foamy or xanthomatous appearance, this variant is characterized by xanthomatous cells that predominate within a fibrous stroma of collagen bundles (4). The most important diagnostic aspect with this particular subtype is to distinguish it from other more invasive forms of fibrohistiocytic tumours, such as dermatofibrosarcoma protuberans (DFSP), malignant fibrous histiocytoma (MFH), and atypical fibroxanthoma (AFX) (5). Positive immunohistochemical staining for Factor XIIIa, present in normal populations of dermal dendrocytes, can be used to distinguish XDF from DFSP and MFH (6). However, a positive result is not specific for dermatofibromas, as AFX and other inflammatory conditions

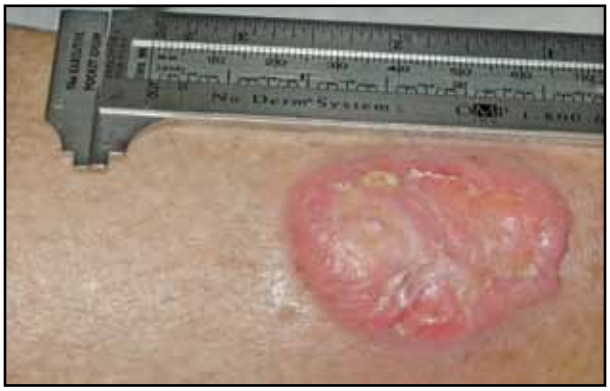

Figure 1: Gross view of a xanthomatous dermatofibroma found on this patient`s left lower leg, measuring 4.5 x 3.2 cm in diameter.

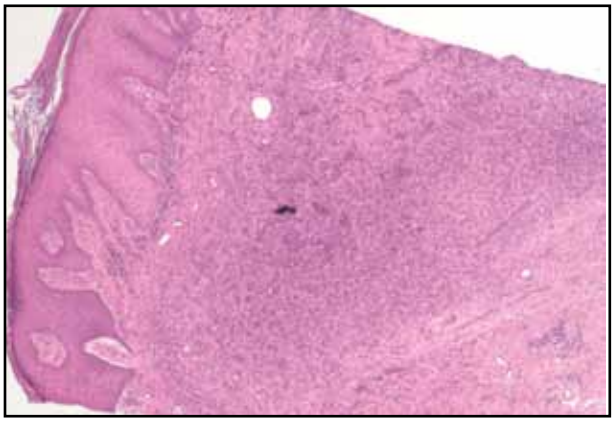

Figure 2: H and E stain of biopsy from centre of the lesion. Low power magnification view. Note the marked acanthosis and hyperkeratosis of the epidermis.

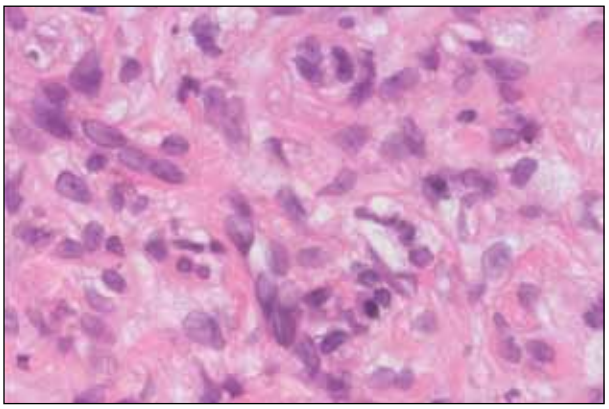

Figure 3: H and E stain of biopsy from centre of the lesion. High power magnification view. Evident are the foamy, spindle shaped cells, scattered between dense collagen bundles.

also can demonstrate XIIIa positivity (6). Thus, histologic examination must be used to further distinguish XDF from AFX. The benign nature of XDF is apparent histiologically, as the variant is characterized by well differentiated cells with little pleomorphism and mitotic activity, in contrast to the high degree of mitotic activity and atypical mitosis observed in AFX (3,7).From a clinical standpoint, the ability to distinguish xanthomatous dermatofibroma is very important, as an incorrect interpretation could result in inappropriate treatment.

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CASE REPORT

14,000 Volt Electrical Injury to Bilateral Upper Extremities: A Case Report

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ABSTRACT: Electrical burns are among the most devastating of burn injuries. High voltage electrical injuries result in extensive deep tissue damage and are associated with multiple complications, long term morbidity, and a high mortality rate. We describe the case of a 47 year-old electric company linesman who suffered a high voltage electrical injury (HVEI) of 14,000 volts to bilateral hands and wrists managed by the Division of Plastic and Reconstructive Surgery at the McGill University Health Center in Montreal, Quebec, Canada. His management included multiple operative procedures, including escharotomies, fasciotomies, serial debridements, and bilateral pedicle groin flaps, and amputation of his left hand.

KEYWORDS: High-voltage, Electrical Injury, Escharotomy, Fasciotomy, Amputation.

INTRODUCTION

Electricity is omnipresent in our daily lives. Unfortunately, electrical injury can result in some of the most devastating thermal traumas. As opposed to thermal burns, the cutaneous burn size does not correlate with the extent of damage seen in high-voltage (>1000 V) electrical injuries; electrical injuries result in extensive deep tissue injury in addition to various other systemic complications. Morbidities, prolonged hospital stay, multiple visits to the operating room, and long rehabilitation process are not uncommon with these types of injuries.

CASE STUDY

A 47 year-old Caucasian male, working as an electric company linesman, was transferred to the Montreal General Hospital following a work-related high-voltage electrical injury (HVEI). While working near high tension power lines, he lost balance and accidently grabbed hold of a wire running 14,000 V with both hands. He was subsequently thrown from the source, fell approximately twenty feet, and suffered blunt head trauma resulting in loss of consciousness.

On arrival to hospital, the patient was alert, oriented and hemodynamically stable. He had 3% visible total body surface area burns involving bilateral wrists circumferentially and bilateral hands (Fig. 1). This consisted of third degree burns to

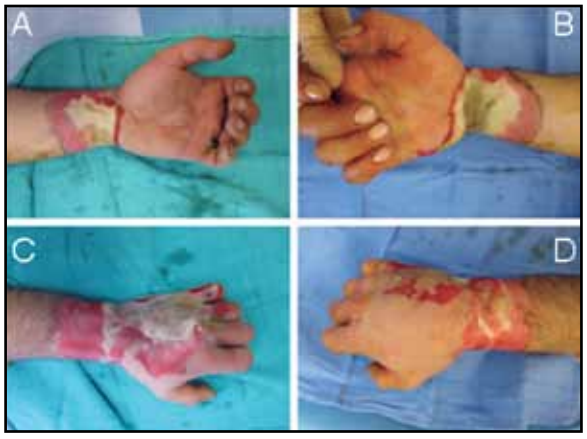

Figure 1: Images on day of admission taken in the operating room. Images A & B show the volar aspects of the left and right wrists, respectively. Images C & D show the burns extending onto the dorsal surface of the left and right hand, respectively.

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the volar aspects of both wrists, and second degree burns to the dorsal aspects of both wrists and hands with digits and palms relatively sparred. CT scan of the head revealed a left frontal bone comminuted fracture and a left subdural hematoma with a 3mm shift. The patient was immediately taken to the operating room by the neurosurgery team for left frontal craniectomy. In addition, he presented with myoglobinuria and a creatine kinase of 32 000 U/L and thus copious intravenous hydration was begun.

Within hours of presentation, he was found to have elevated compartment pressures in both hand (100 and 70 mmHg on the right and left, respectively) and wrists (91 and 75 mmHg on the right and left, respectively) and was immediately taken to the operating room for bilateral hand and wrist escharotomies and fasciotomies (Fig. 2). Subsequently the patient was taken back to the operating room for serial debridements of necrotic tissue. MRI with gadolinium was performed to delineate the extent of deep tissue injury. Imaging had shown extensive tissue necrosis extending from the distal third of the forearm to the level of the wrists bilaterally, involving both extensor and flexor compartments (Fig. 3).

Despite escharotomies, fasciotomies and serial debridements the patient's left hand became progressively congested with poor doppler signals and low O2 saturation within each digit. On post-burn day 16, 9 days since the last debridement, the hand became cold and did not return blood on pinprick in any of the digits. Later that night, the patient was taken to the operating room for amputation of the left hand. After amputation, the patient was left with significant soft tissue defects to bilateral wrists and hands. Bilateral pedicle groin flaps were used for coverage of the defects as well as to increase vascularity to the region (Fig. 4a). Fourteen to twenty-one days after inset of the flaps, the flaps were ready to be separated; final results are shown in Figure 4b and 4c.

In summary, the patient remained in hospital for a total of 81 days, 65 of which were spent in the ICU. He was taken to the operating room a total of 7 times for escharotomies, fasciotomies, and serial debridements of bilateral hands and wrists, as well as amputation of his left hand and the necessity of tissue transfers, in the form of pedicle groin flaps, for soft tissue coverage. His course was complicated by rhabdomyolysis with a creatine kinase level peaking at 52 235 U/L, which was successfully managed with copious intravenous hydration and diuresis. The patient is currently rehabilitation center, working extensively with physiotherapy for elbow and shoulder mobility. Future plans include extensive tendon transfers to the right hand for improved function.

DISCUSSION

It is reported that electrical burns constitute between 0.04% to as high as 32.2% of admissions to major burn centers (1, 3-6). Mortality rates are significant with these types of injuries, reported in the literature to be as high as 59% (1); the most common cause being secondary to an acute arrhythmia at the scene of the injury(2). They account for approximately 1000 deaths each year in

Figure 2: Post-fasciotomy images of the patient in the operating room. Images A & B showing wrist fasciotomy, thenar incisions, and carpal tunnel release of left and right hands and wrists, respectively. Images C & D show fasciotomy incisions on the dorsal aspect of left and right wrists, respectively, as well as the longitudinal metacarpal incisions of the hands.

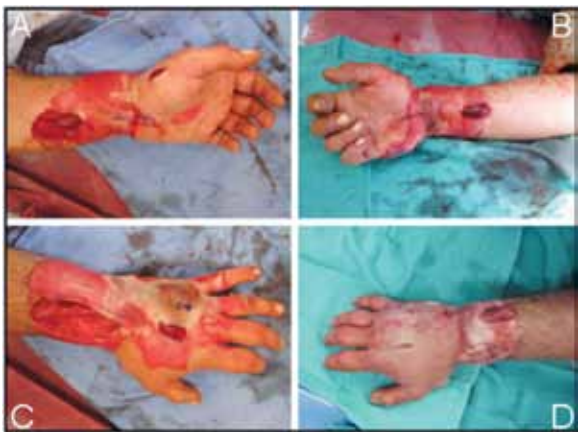

Figure 3: MRI with gadolinium of left wrist and forearm. The image of left forearm demonstrates the extensive non-enhancing muscles from the distal third of the forearm to the level of the wrist suspicious for myonecrosis involving both extensor and flexor muscles.

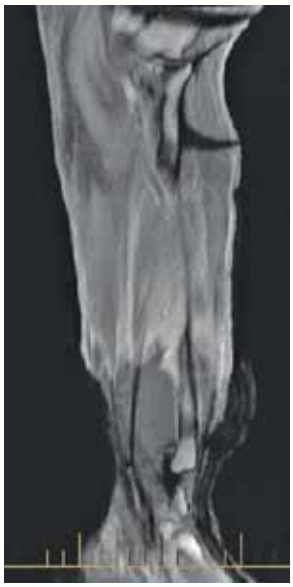

Figure 4: Pre and post separation of pedicle groin flap to bilateral wrists. Image A shows the patient with bilateral pedicle groin flaps attached to bilateral wrists. Image B shows the amputated left hand once flap was separated and inset. Image C shows the right hand after flap separation.

the United States alone, ranking 5th as the most common cause of occupational deaths (3). Electrical burns are most commonly seen in work related injuries and involve mainly young males. Electrical company linesman, electricians and construction workers are especially at risk (4, 5). Sadly, it has been reported that as little as 5.4% of patients suffering a HVEI are able to return to their previous line of work (2). This can likely be attributed to the fact that these injuries commonly involve the hands and upper extremity (4, 5).

Contrary to thermal burns, high-voltage injuries result in extensive deep tissue damage, extending far beyond what can be predicted by TBSA involved, and resulting in higher rate of complications (6). In a case-matched controlled analysis comparing HVEI and thermal burns, Handschin et al. (6) found a significantly higher rate of escharotomy/fasciotomy (47% vs. 21%), amputations (19.1% vs. 1.5%), as well as total hospital length of stay (44 days vs. 31 days) in HVEI versus thermal burns.

Commonly seen with HVEI are associated acute injuries which include fractures, head trauma, intra-abdominal injury, renal injury, soft-tissue injury, and acute ocular injury. Associated injuries have been described to occur in 25.1% of HVEI (5, 8). In addition to associated trauma, patients suffering HVEI are prone to various complications as well. In a study involving 202 electrical injuries, neurologic complications, deep muscle involvement, and amputation of extremities were found to be the most prevalent (4). Similarly, Arnoldo et al. found amputation of extremities or digits and muscle necrosis to be some of the most frequently observed complications, observed in 95 and 68 of the 263 cases of HVEI, respectively (5). As presented in our case, myoglobinuria and fasciotomy are also commonly encountered complications. In the current literature, escharotomy/fasciotomy rates have been described to be as high as 54% (7) and amputation rates as high as 49.4% (2).

Interestingly, Cancio et al. found myoglobinuria to be a factor associated with the need for fasciotomy. Furthermore, they had found myoglobinuria and the need for fasciotomy to be independent risk factors for amputation. Using an equation derived to predict the probability of amputation (8), the patient from our case had a 94.98% probability of requiring an amputation.

HVEI are devastating injuries associated with a vast array of serious and inevitable complications. The prognosis for these patients depends on the degree of the initial insult as well as the severity of any subsequent complications. Early intervention is the goal with resuscitation and aggressive surgery being the mainstay of management. Considering that most HVEI are work-related, the best way to decrease the morbidity and mortality related to these injuries is prevention. Through public education and work safety programs, most electrical injuries can be avoided.

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CASE REPORT

Use of fresh osteochondral allograft in repair of distal femur after trauma

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Jennifer E. Taylor, Allan E. Gross

ABSTRACT: Preserving the ability to maintain an active lifestyle is a major concern in the reconstruction of the knee in young patients. For the healthy individual who desires to maintain a relatively active lifestyle, fresh osteochondral allografts may serve as an alternative to total joint reconstruction. The use of fresh allografts is primarily indicated in the patient suffering from a traumatic loss of articular segments, who is too young or active for arthroplasty. In addition, fresh osteochondral allografts have a number of advantages over arthroplasty such as providing surgeons with a source of large grafts that can be fitted to replace osteochondral defects and cover the majority or entirety of articular surfaces without any donor site morbidity. In this case, a young, active patient lost a 7 x 8 cm portion of their distal femur, including a large portion of the articulating surface. Using a fresh osteochondral allograft, harvested within 24 hours of donor death, a segment was fitted to match bony apposition, articular congruity, and congruity with the femoral notch and affixed with four partially threaded cancellous screws. Joint function was restored with the allograft in place, allowing the patient to delay the need for a total joint replacement.

KEYWORDS: Allograft, Osteochondral, Trauma, Joint Reconstruction, Knee

INTRODUCTION

Reconstructing the knee in young, active patients is a major challenge in orthopaedic surgery. Repair techniques for cartilage and osteochondral defects include microfracture, osteochondral autograft, osteochondral allograft, and autologous chondrocyte implantation. The use of fresh allografts is mainly indicated in the patient suffering from a traumatic loss of articular segments who is too young or active for arthroplasty. In addition, fresh osteochondral allografts have a number of advantages over arthropasty including the absence of donor site morbidity, while providing surgeons with a source of large grafts that can be fitted and sized to replace osteochondral defects larger than 3 cm in diameter and 1cm deep or entire articular surfaces (1). The ability to shape the allograft to fit the individual allows for the reconstruction of a wide variety and shape of osteochondral defects. Both tibial and femoral defects can be treated, and if required, the allograft meniscus can also be transplanted along with the osteochondral graft (2). Circular femoral allografts are usually put in place using press-fit technique. In instances where the allograft covers a large surface area, as in this case of a femoral condyle or tibial plateau, cortical screws can be used, especially if osteotomy realignment is necessary to unload a compartment (3, 4).

Allografts are provided either as frozen tissue recovered from donors and cryogenically prepared for future use or as fresh tissue recovered and immediately used. Both types are irradiated to

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eliminate the transmission of viral and bacterial infections. If harvested within 24 hours of death and preserved at 4 degrees Celcius after irradiation, fresh avascular osteochondral allografts show a 100% chondrocyte viability after 4 days (5, 6, 7). No anti-immunogenic drugs are administered. The thick extra-cellular matrix surrounding the chondrocytes isolates them from contact with host cells (8), but if the graft is frozen in an effort to further reduce immunogenicity, chondrocyte viability is compromised (9, 10). After implantation chondrocytes have been shown to remain viable for the life of the allograft. Cartilage being alymphatic, aneural and avascular unlike other transplanted tissues, eliminates the concern for vascularization after implantation. Long-term chondrocyte viability has been confirmed in multiple reports including case studies after 17, 25, and 27 years (11, 12, 13, 14, 15, 16).

In this case report we describe the use of fresh osteochondral allografts to repair trauma to articulating surfaces, providing an alternative to treating these injuries with a prosthetic. In this way, joint function can be restored delaying the need for a total joint replacement in the young and active patient.

CASE STUDY

A 30 year old male was recreationally riding a snow mobile when he experienced a traumatic accident. The left knee was fractured severely through the anterior aspect of his distal femur in the coronal plane. A fragment of the distal femur was contaminated and lost at the scene. In addition, his quadriceps were lacerated. A repair of his quadriceps mechanism was carried out immediately following the incident, requiring a free latissimus dorsi flap for soft tissue coverage. Following the initial surgery, the patient was able to walk and bend his knee, but suffered from pain radiating to the anterior aspect of the knee. Upon examination, the wound was healing well and the previous free flap to the anterior aspect of the knee appeared healthy. Knee joint range of motion was limited to 0 to 60 degrees. Neurovascular exam was unremarkable. After examination the patient was scheduled for a fresh osteochondral allograft to correct the bone loss in the anterior femur. Pre-operative radiographs were taken to plan the operative requirements of the patient (figure 1). As the preoperative radiographs did not indicate any angular deformity in the leg on 4-foot standing views, an osteotomy was not planned. The surgery was conducted 7 months following the traumatic incident.

Operative Technique

The previous trauma and surgery with subsequent scar tissue was considered when planning the incision site. The incision was made longitudinally over the anterior distal femur, curving medially around the medial aspect of the previous latissimus dorsi graft. A medial parapatellar arthrotomy was performed. Due to the great deal of scar tissue encountered on the inferior aspect of the patella,

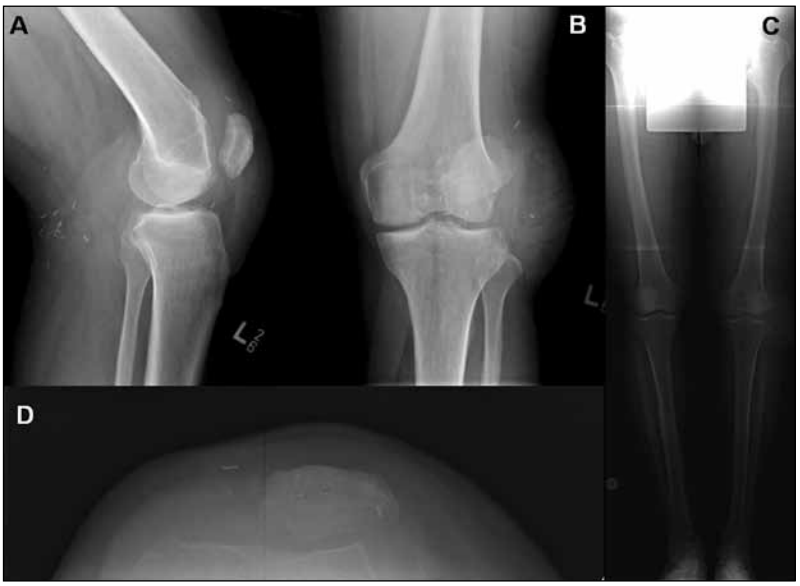

Figure 1: Preoperative x-rays including coronal (A) and sagittal (B) aspects about the left knee. Four-foot standing x-rays (C) were also taken to evaluate joint angulation. Axial x-rays through the defect and patella were also taken to depict the defect size and location as well as the placement of the patella.

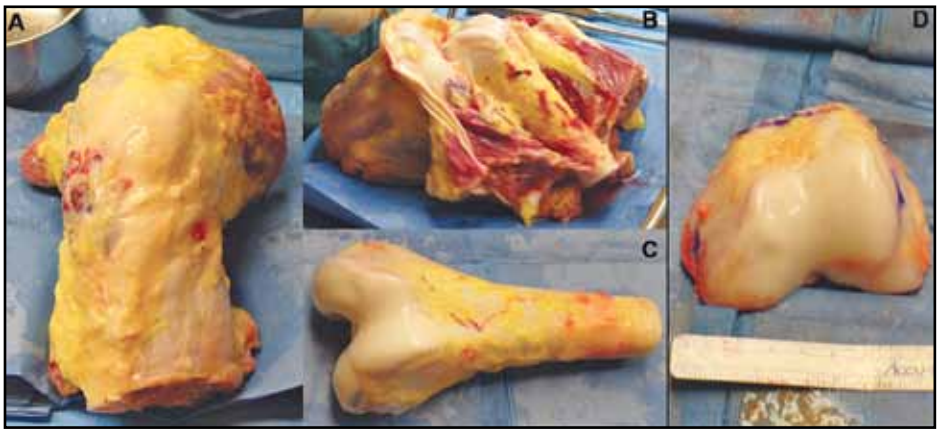

Figure 2: The preparation of the received allograft (A) included the removal of soft tissue and musculature (B) down to the articular surface without damaging the cartilage (C). The allograft was sized to the defect and excess bone was removed using an oscillating saw (D). Any further measurements were made by re-sizing the allograft directly against the defect site and making additional adjustments with the oscillating saw.

an incision through the anterior medial third of the patellar tendon was used to gain access to the joint space. This was repaired with a Kessler stitch following the procedure.

Following the arthrotomy, scar tissue was cleared off the anterior aspect of the distal femur down to bleeding bone. The defect was measured to be 7 cm in the mediolateral plane, and 6 cm from anterior to posterior in the coronal plane beginning from the top of the femoral notch to the top of the defect. These measurements were used to model the allograft. After the removal of scar tissue, the knee was flexed to approximately 70 degrees. In this position, an oscillating saw was used to level the defect plane in order to attain a flat surface to affix the allograft flush with host bone.

The fresh osteochondral allograft was obtained according to the procedures established by the American Association of Tissue Banks (17). The allograft was irradiated with 2.5 Mrad (25,000 Gy) in the hospital bone bank, and consequently stored at -70 degrees Celsius. To maximize cartilage quality, the donor chosen was less than 30 years old. The graft was procured within 12 hours of death, excising the entire joint including the capsule and ligaments under strict aseptic precautions. Bacterial, fungal and mycobacterial cultures were taken before the joint was submersed in Ringer's solution containing 1g/l of cefazolin and 50,000 units/L bacitracin and sealed in a container. The container was then wrapped in sterile towels and plastic bags and stored at 4 degrees Celsius until use. The allograft

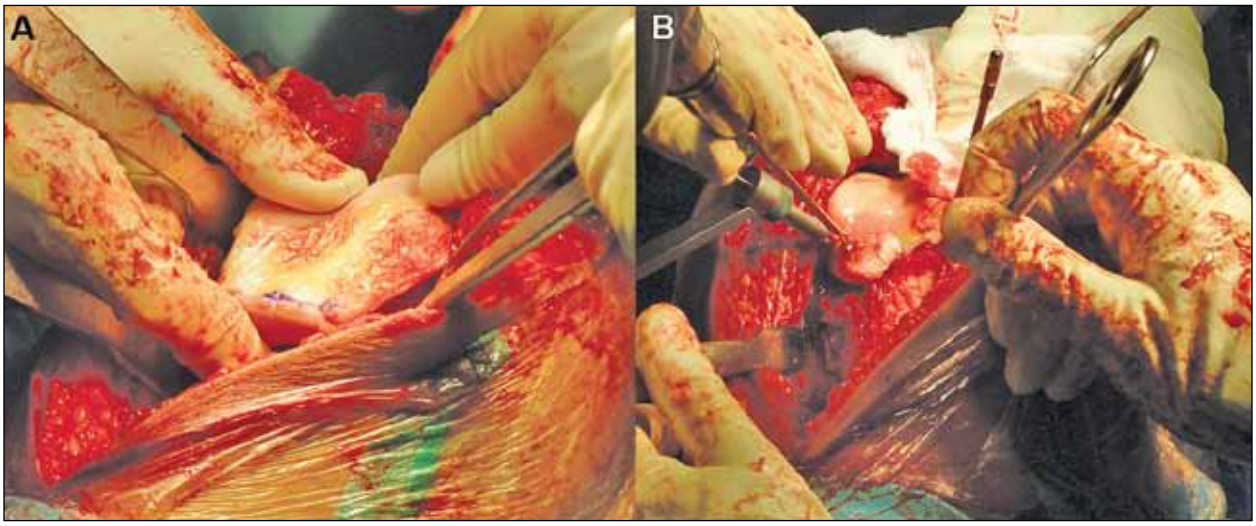

Figure 3: Once the allograft was sized against the defect site (A), ensuring that bony apposition, articular congruity, and congruity with the femoral notch had abeen achieved, the allograft was carefully affixed to the distal femur using four 6.5 mm partially threaded cancellous screws (B).

was initially prepared on a separate table using an oscillating saw while intraoperative measurements were taken about the defect site. Outer musculature about the allograft was removed with special care given to avoid damaging the allograft articular surface (figure 2). Final adjustments were made by sizing the graft directly against the patients defect site (figure 3A). Throughout preparation of the allograft, it was irrigated with Bacitracin solution. Once the desired fit was achieved, including bony apposition, articular congruity, and congruity with the femoral notch, the graft was affixed to the distal femur using four 6.5 mm partially threaded cancellous screws (figure 3B). After fixation, intraoperative radiographs were obtained confirming good position. Following radiographs, tracking of the patella was physically examined with careful attention to ensure there was no lateral subluxation. The entire wound was irrigated with Bacitracin solution before closure. Again, a Kessler stitch using a 2-0 Vicryl suture was used to close the opening made in the patellar tendon. The repair held after knee flexion to 90 degrees.

DISCUSSION

Postoperative management included keeping the patient in an immobilizer, but improvements in passive range of motion upwards of 90 degrees of flexion resulted. Passive range of motion exercises were encouraged while the patient remained on site. At the time of discharge, the left lower extremity was neurovascularly intact and no evidence of infection was observed. At this time, the patient was ambulating well using crutches with emphasis on avoiding weight-bearing. Another set of post-operative x-rays confirmed the placement and attachment of the allograft before the patient returned home (figure 4). At this time, the patient began a rigorous yet conservative physiotherapy program to regain function of the left leg. Due to the severe amount of trauma inflicted on the musculature about knee joint a well planned program is of utmost importance. In cases as this, the trauma an abundance of scar tissue may make progress in knee flexion and range of motion more difficult. Our patient was young and very determined to regain full use of the leg. Despite the damage to the quadriceps and the build-up of scar tissue, he progressed very quickly regarding improvements in range of motion. One month post-op, passive range of motion had improved to 112 degrees and quadriceps muscle strength had improved greatly. The patient could fully ambulate unassisted with only a slight limp and had significant reduction in joint pain. At this time he continued physiotherapy geared towards optimizing gait and quadriceps strength. With continued physiotherapy for the soft tissue damage, further improvements allowed the patient to return to light recreational activity.

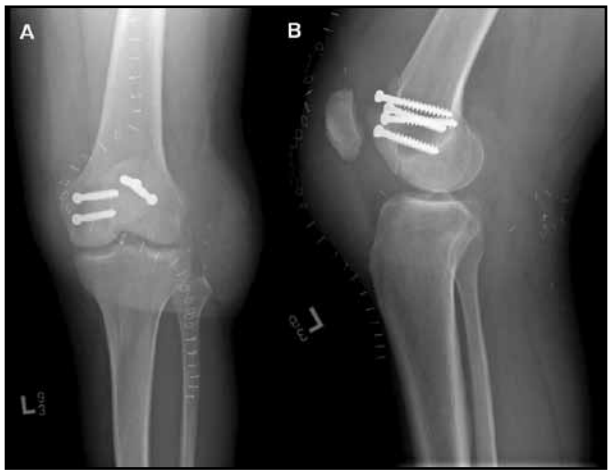

Figure 4: Postoperative x-rays were taken at the time of surgery and as depicted here, one week after surgery before final discharge. Sagittal (A) and coronal (B) images were taken about the left knee to ensure proper placement and fixation of the allograft. Note the proper placement of the patella in the patellar groove.

The use of fresh allografts is mainly indicated in the patient suffering from a traumatic loss of articular segments deemed too young or active for arthroplasty. Allograft has been used to treat conditions in addition to tramatic injury. The use of fresh osteochondral cadaveric allografts for conditions including unicompartmental osteoarthritis, steroid-induced avascular necrosis of the femoral condyles, osteoarthritis dissecans, and traumatic defects has shown encouraging mid- and long-term results (18, 19, 20, 1, 21, 22, 23, 24, 25, 26, 27, 28, 29). These clinical evaluations have demonstrated a reduction in joint pain, allograft-host bone healing an improved weight bearing. Grafts performed secondary to trauma have the most promising results, while grafts for degenerative disease have had the worst (25, 29). At our institution, osteochondral allografts are not used currently for treating osteoarthritis or osteonecrosis that is steroid-induced or occurs spontaneously with inflammatory arthropathy. Patients under the age of 60 have been reported to have better results with allografts than those above (24). In addition, the use of allografts for bipolar defects across the femur and tibia have not been as successful as unipolar transplants (19). In a recent study of survival rates of fresh femoral osteochondral allografts, 74% of grafts survived at 15 years with 61% of the patients having excellent to good functional outcomes (1). Some of the failures

included were due to the development of degenerative joint disease (osteoarthritis).

Aside for the limitation in situational use, there are a number of disadvantages for using fresh osteochondral allografts. Large shell allografts are in limited supply, and patients much wait until a cadaveric allograft becomes available (30). In addition, it is necessary to use a highly organized transplant service because of the concern for disease transmission. The risk for transmission is similar to that of homologous blood transfusion, although lower estimates have been published (31). Donor osteocytes do not survive without vascularization. The heightened immunogeneic response this may induce is not countered with immunosuppressive drugs and not considered necessary. In histopathologic analysis of failed osteoarticular shell allografts between 12 and 84 months after transplantation, no evidence of transplant rejection was detected (32). For the healthy patient, who desires to maintain relatively active lifestyle, fresh osteochondral allografts may serve as an alternative to total joint reconstruction. Here, a young, active patient lost a 7 x 8 cm portion of their distal femur, including a large portion of the articulating surface. Using an allograft, joint function was restored, while allowing the patient to delay the need for a total joint replacement.

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ORIGINAL ARTICLE

Crohn's disease presenting with atypical mucocutaneous lesions in an 11 year old boy

Michael Sidiropoulos, Beth Skuy*

CASE REPORT

In April, an 11-year-old boy presented to our clinic with neck and anterior chest pain of 1 week's duration. Presenting symptoms included dysphagia and odynophagia. The patient's height and weight were in the 75th and 50th percentile respectively, and he had had stable growth since birth. His weight at presentation was 88 lbs. He was subsequently referred to a paediatrician who described a low-grade fever, occasional chills, decreased appetite, and difficulty swallowing both liquids and solids. At that time, while there was no cervical lymphadenopathy, he did have a few shallow ulcers on his lips. Within days, the patient developed periorbital edema, a small erythematous patch on the lateral surface of his left arm, and five, faint, mildly tender erythematous lesions on the fingers of his left hand. Examination of his oral cavity revealed extensive flat, erythematous vesicular-like lesions clustered on the midline of his lower lip, some of which had erupted to form ulcers. There were no other significant findings and the patient's past medical history was unremarkable. The patient was fully immunized and had no allergies. Laboratory investigations, including basic haematological and microbiological examinations, parasitology and urinalysis, yielded normal results. An x-ray of his neck and chest were normal, as was an upper GI series. An eye examination showed aseptic conjunctivitis.

The patient was subsequently evaluated by the department of Rheumatology at the local Children's Hospital and was diagnosed with "query Kawasaki disease," despite the insidious course of the illness. After receiving a course of intravenous gamma-globulin, his symptoms quickly resolved and he was discharged home on low-dose Aspirin. He continued the Aspirin and was seen in the Pediatric Cardiology Clinic for follow-up 2 months later. Physical examination and an echocardiogram revealed no evidence of coronary involvement and the Aspirin was discontinued. The patient's weight had decreased to 85 lbs. Unfortunately, the patient complained of upper quadrant pain and fatigue on a daily basis throughout the summer and was seen by a paediatrician in October. His mother stated that his oral intake had decreased and he experienced occasional abdominal cramping following meals. Despite sleeping normally, the patient had decreased energy. There had been no fever, joint pain, rash or oral-ulcers. Bowel movements were

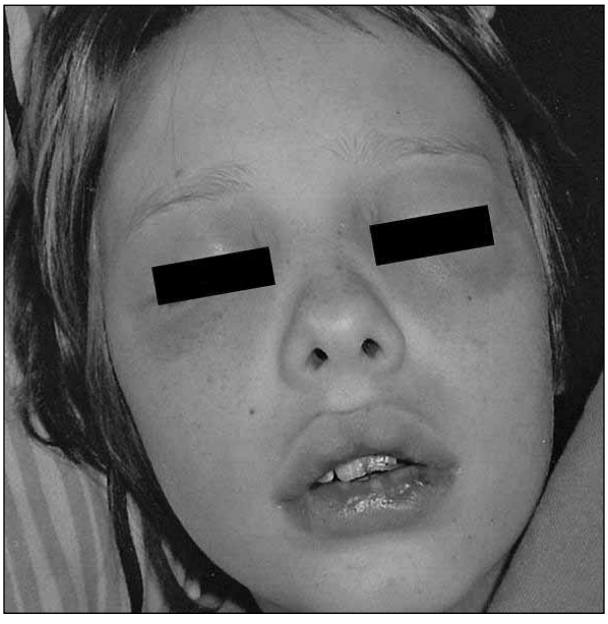

Figure 1. Extensive flat erythematous vesicular-like lesions are evident on the lower lip and periorbital erythema and edema is seen bilaterally. The patient complained of dysphagia and odynophagia.

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normal, with no blood in the stool and only occasional diarrhea. The patient was diagnosed with gastritis secondary to Aspirin use or cholelithiasis, since Kawasaki Disease can temporarily elevate lipids and triglycerides. A one month trial of Rabeprazole 20 mg p.o. daily was prescribed. Blood work and an abdominal ultrasound were ordered and follow-up was scheduled within 1 month.

Two weeks following his presentation to the paediatrician's clinic, the patient presented to the local Children's Hospital with a sudden onset of severe right lower quadrant abdominal pain. He had a history of abdominal pain, anorexia and low grade fever for 3 days prior to presentation. An abdominal ultrasound revealed a perforated appendix with an abscess. He was admitted to hospital and put on Ampicillin, Gentamicin and Metronidazole. An abdominal CT scan showed a thickened appendix with an appendicolith present. There was also thickening of the terminal ileum and evidence of a fluid-filled abscess. Interventional Radiology was consulted and a drain was inserted to drain the abscess.

The Gastroenterology Service suggested that inflammatory bowel disease (IBD) might be a possibility, as additional information from the patient's mother revealed that her second cousin had Crohn's disease. Upon further investigation, the patient had an elevated erythrocyte sedimentation rate of 53 mm/hr and a C-reactive protein of 26.9 mg/L. Albumin and total protein were both normal at 35 g/L and 80 g/L respectively. The patient weighted 81 lbs. A fistulogram was negative and the antibiotics were stopped after a total of 9 days. The patient returned to baseline and was scheduled for follow-up in the IBD Clinic within 2 weeks.

On presentation to the IBD clinic in November, the patient was still experiencing fatigue, poor appetite, and had some intermittently loose stools. There was no blood present in the stools. Physical examination was normal, except for mild clinodactyly. Diagnostic imaging revealed that the terminal ileum had mucosal irregularity in a "cobblestone" pattern. In addition, there was separation of adjacent bowel loops from the terminal ileum, with possible thickening of mesentery. A diagnosis of Crohn's disease was subsequently made. The patient was started on a course of prednisone which resulted in moderate relief of the gastrointestinal problems and stabilization of the patient's symptoms. Methotrexate or Immuran were subsequently added to the patient's regimen.

DISCUSSION

Crohns disease is a gastrointestinal disorder in which any part of the alimentary tract may become inflamed, from the mouth to the anus. The disease is characterized by relapsing and remitting signs and symptoms, the most common of which are abdominal pain, diarrhea, fever, and weight loss. However, there are numerous extraintestinal features, such as arthritis, iritis, and mucocutaneous lesions (1). Mucocutaneous lesions, although not considered part of the classic triad of fever, abdominal pain, and diarrhea, may be more common than previously thought. Mucocutaneous lesions have been reported to occur in 10% to 44% patients (2-5). Some of the more common lesions include erythema nodosum, pyoderma gangrenosum, Sweet syndrome, epidermolysis bullosa acquista and clubbing (6). Numerous oral lesions can also be present. These can include cobblestoning, mucosal tags, pyostomatitis vegetans and orofacial granulomatosis (7-9). Nonspecific lesions, such as aphthous ulcers, labial and facial edema and gingival erythema and edema are also common (9-11). These lesions are also known to precede gastrointestinal symptoms in patients with Crohn's disease (19,12,13). Numerous studies have shown that oral lesions are often the initial presenting sign/symptom of IBD, particularly in children (8-10,12,13). A study by Barnard and Walker-Smith found that 80% of pediatric patients with Crohn's disease had oral lesions (14). A study by Galbraith et al described 8 pediatric patients with asymptomatic Crohn's disease who presented with mucocutaneous lesions, of which the majority were oral and perianal lesions (9). The patient's ages ranged from 3 to 14 years old and common presenting lesions were lip swelling, oral ulcers or erosions, pyoderma gangrenosum and gingival edema. Many of these patients were also found to have perianal lesions, such as fissures, fistulas, and/or skin tags; however, in only 2 of the 8 patients was this one of the presenting complaints. The time to diagnosis of Crohn's disease after initial presentation with mucocutaneous lesions ranged from 3 months to 42 months. All patients within this study denied any gastrointestinal symptoms. We report a case of a pediatric patient who presented with mucocutaneous lesions, and was initially diagnosed with Kawasaki's, but was subsequently found to have Crohn's disease. Similar to previous reports, we suggest that Crohn's disease is a common cause of mucocutaneous lesions and that unexplained mucocutaneous lesions in a pediatric patient should alert the physician to further examine the patient to rule out Crohn's disease (8,9,14).

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CASE REPORT

ICA Occlusion by an ACTH-secreting pituitary adenoma post-TSS and irradiation

Diala El-Zammar*, Ryojo Akagami

ABSTRACT: Occlusion of intracranial arteries by a pituitary adenoma with ensuing infarction is a rare occurrence. In this case study, we show the instance of a pituitary macroadenoma and apoplexy causing mechanical obstruction of the internal carotid artery with consequent infarction following transphenoidal surgery (TSS) and radiation therapy in a patient with Cushing's disease. We report a 44-year-old woman presented with amenorrhea and headaches. Necessary investigations, resection by TSS, and microscopic examination revealed an adenocorticotropin (ACTH)-secreting pituitary macroadenoma. The pituitary tumour recurred in subsequent years, resulting in the development of Cushing's disease and syndrome. Despite two more transphenoidal surgeries, radiotherapy, and medical suppressive therapy, the pituitary adenoma continued to enlarge, and the hypercortisolemia and Cushingoid symptoms persisted. A craniotomy was arranged as the next step in the treatment strategy. Only hours prior to the scheduled surgery, the patient developed left-sided hemiplegia, was diagnosed with acute occlusion of the right ICA and underwent an emergency bifrontal craniotomy with evacuation of the tumour and decompression. Pathological examination revealed evidence of apoplexy in the ACTH-secreting pituitary adenoma. This case demonstrates the vast scope of complications that can arise from pituitary adenomas despite combination therapy and forewarns clinicians to be prepared to manage these infrequent but conceivable occurrences.

KEYWORDS: Pituitary adenoma, Cushing's disease, pituitary apoplexy

INTRODUCTION

Adenocorticotropic hormone (ACTH)-secreting pituitary macroadenomas causing Cushing's disease is a rarity with an incidence of 0.7 to 2.4 cases per million inhabitants annually (1-3). Cushing's disease (CD) is a debilitating endocrinopathy that, for the clinician, is a challenge to diagnose and treat. The current treatment of choice for CD is transsphenoidal pituitary surgery (TSS), which is associated with long-term remission rates of 64–93%. Lower range success rates are found in patients with pituitary macroadenomas as compared to those with microadenomas (4-13). Current published literature has established that the mortality rate of TSS is less than 1%, and morbidity is approximately 1.8% (1,5,12,14,15). A multiple modality approach, including surgery, radiotherapy, radiosurgery, and adrenalectomy, for the management of CD due to ACTH-secreting macroadenomas has also been shown to be effective (1). Despite the comprehensiveness of this therapeutic strategy, disease recurrence and persistence rates are still higher for macroadenomas than microadenomas; this is likely due to the invasive nature of macroadenomas (1).

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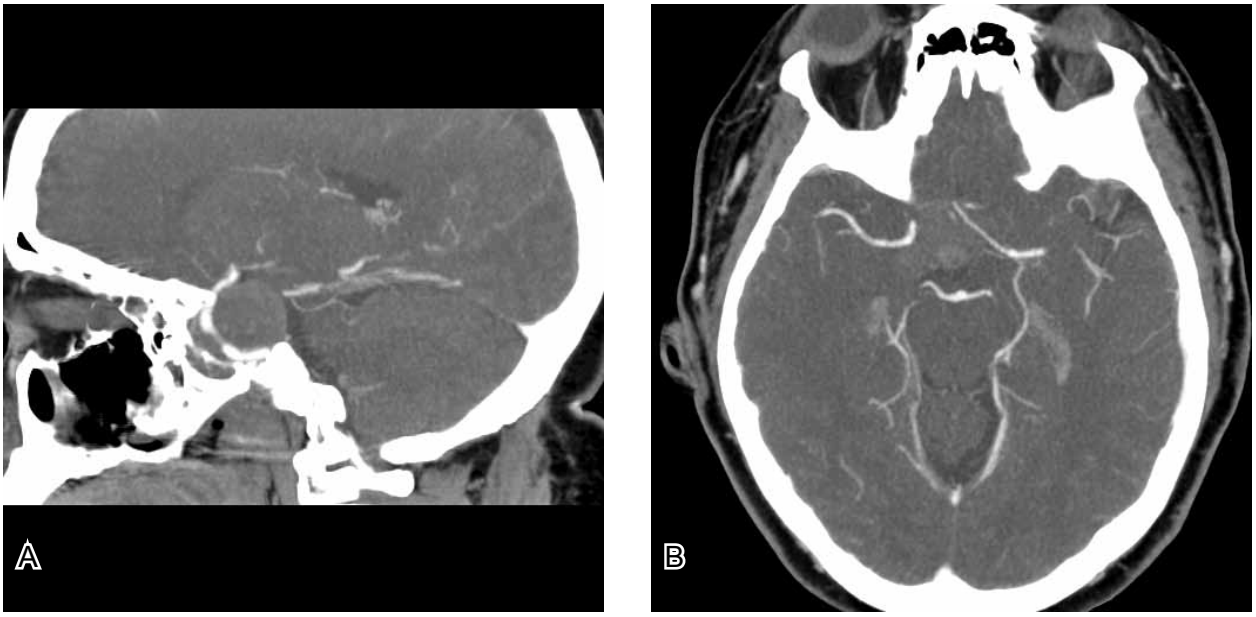

Figure 1: Pre-operative contrast-enhanced CT head showing a patent right carotid artery. CT scan also shows a well-circumscribed pituitary tumour measuring 3.3 x 4.3 x 3.9 cm with suprasellar extensions and marked elevation of the chiasmatic tissue. The arterial phase imaging demonstrates the right internal carotid artery to have a mildly redundant loop situated at the junction of its precavernous and cavernous segments due to mass effect upon the vessel by the tumour. The radiologist attributed the reduced calibre of the right ICA to possible stenosis. On the left, the ICA is not found to be as significantly displaced as on the right. (a) Sagittal view. (b) Axial view.

Complications can arise from pituitary adenomas as a direct result of the tumour itself or as a consequence of the treatment. Functional pituitary adenomas will be symptomatic in accordance with the type and quantity of the hormone they elaborate (16). For example, a prolactin (PRL)-secreting adenoma may present with infertility, galactorrhea, amenorrhea and decreased libido, while an ACTH-releasing adenoma involves weight gain, hypertension, diabetes, excessive hair growth, abdominal striae, and lipodystrophy of face and back. Likewise, a growth hormone (GH)-secreting tumour may present with acromegaly and gigantism, in contrast to a thyroid-stimulating hormone (TSH)-producing adenoma which causes tachycardia, palpitations, weight loss and heat intolerance (16).

Functional pituitary adenomas can secrete Although some functional pituitary tumours grow large enough to compress adjacent structures causing neurological symptoms and compromise of normal pituitary function, functional adenomas are less likely than non-functional tumours to do so (17). In rare cases, these tumours may spontaneously hemorrhage or become infarcted (18), a condition known as pituitary apoplexy. Some uncommon postoperative complications include infection, cerebrospinal leakage, vascular injury, double vision, visual loss, and pituitary deficiency (17). Two very rare post-TSS complications have been reported; one of these cases involved a false aneurysm of the cavernous carotid artery, and the other, a carotid cavernous fistula (19). Although there have been rare reports in the literature of pituitary apoplexy and cavernous carotid artery involvement in patients with a pituitary adenoma, there have been no cases reported of pre-operative intracranial artery infarct due to acute compression by a functional pituitary adenoma in a patient with clinical Cushing's disease.

CASE REPORT

A 44-year-old female of Jamaican ancestry presented with amenorrhea and headaches. She was diagnosed with a pituitary macroadenoma in 1998 and subsequently underwent three transphenoidal pituitary resections in 1998, 2002, and 2004. The patient's condition was complicated by Cushing's disease as evidenced by high cortisol levels and Cushingoid features of central obesity, hirsutism, striae, and thinning of the skin. These symptoms were managed by Ketoconazole for a few years. Her cortisol levels, however, continued to increase and the tumour had, as shown on follow-up scans, enlarged in size despite adjuvant radiotherapy treatment in 2005. A craniotomy and orbital osteotomy were arranged as the next course of action. While awaiting surgery, the patient developed some ptosis of her right eye. This, as well as

a three-week history of decreased visual acuity and visual field deficits accompanied by headaches, led her to present herself to the emergency department at Vancouver General Hospital in February, 2007. On examination, she was found to have new right third nerve palsy while scans revealed no obvious hemorrhage or apoplexy within the tumour (Fig. 1). The patient was kept in hospital and surgery was scheduled. On the morning of the scheduled surgery day the patient experienced increasing headaches. Shortly after the neurosurgeon had examined the patient on rounds, she developed drowsiness, disorientation with Glascow Coma Scale (GCS) of 9, and acute left-sided hemiparesis. The GCS is a score between 3 and 15 that provides an objective assessment of a person's state of consciousness, based on their best eye, verbal, and motor responses to stimuli. A GCS score of 8 or less is indicative of severe brain injury; a score of 9-12 is moderate, and one greater than 13 constitutes minor brain injury (17). Urgent evaluation and CT scan revealed an occlusion of the right carotid artery in the cavernous segment (Fig. 2), which had been patent and flowing on a head CT performed upon admission three days earlier (Fig. 1). There was no evidence of any obvious apoplexy or increase in size of tumour depicted on this pre-operative scan (Fig. 2). Acute occlusion of the right ICA was diagnosed and an emergent bifrontal craniotomy with evacuation of the tumour was performed.

Microscopic examination of the pituitary adenoma displayed areas of recent hemorrhage and tumour necrosis, as well as increased nuclear pleomorphism. There was reported fibrinoid necrosis and hyaline degeneration, which are believed to be induced by irradiation. The neuropathologist concluded that the tumour was an ACTH-secreting pituitary adenoma displaying an unusual profile of immunoreactivity for Melan A.

Intra-operatively, a post decompression cerebral angiogram showed that the right ICA was patent (Fig. 3). Non-contrast CT head, done one day post-operatively, demonstrated near total right MCA and ACA territory infarction with sparing of the posterior right temporal territory (Fig. 4). There was also evidence of right cerebral edema, with near total effacement of the right lateral ventricle. Although a mild leftward shift of the anterior midline structures was observed, no transtentorial herniation was seen. Her postoperative course was also complicated by diabetes insipidus, which was treated with DDAVP.

A non-contract CT scan performed eight months later showed reduced mass effect and relief of the previous compression of the right lateral ventricle (Fig. 5). Extensive right ACA and MCA infarction with sparing of the posterior right temporal territory persisted. The CT scan confirmed no midline shift, hydrocephalus, or intracranial hemorrhage. It is noteworthy to mention that MRI investigations

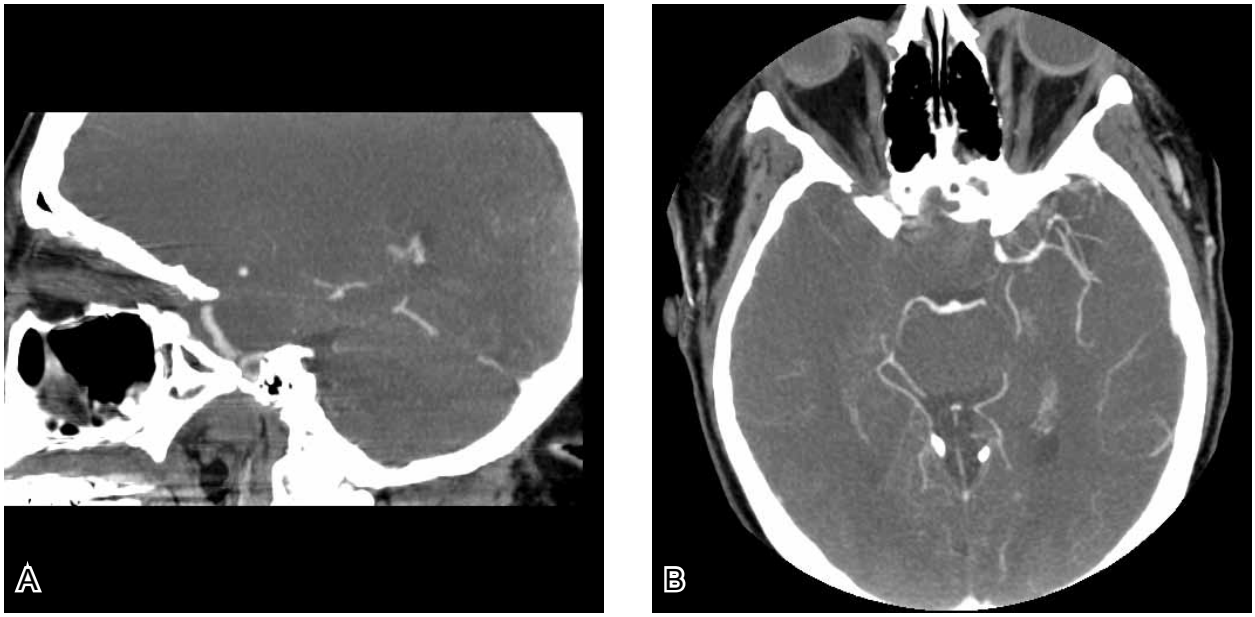

Figure 2: Pre-operative contrast-enhanced CT head on the day of the surgery showing an occluded right carotid artery. The right ICA is severely attenuated and compressed against the right anterior clinoid process by the pituitary mass. A very small right anterior communicating artery is noted with no significant posterior communicating artery seen bilaterally. (a) Sagittal view. (b) Axial view.

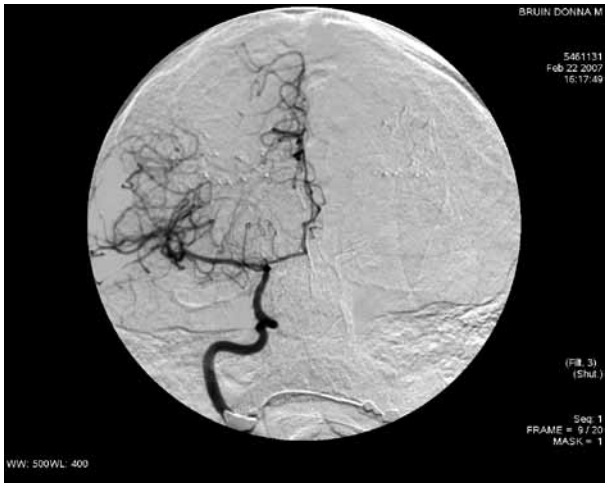

Figure 3: Intra-operative anteroposterior angiogram showing a patent right carotid artery.

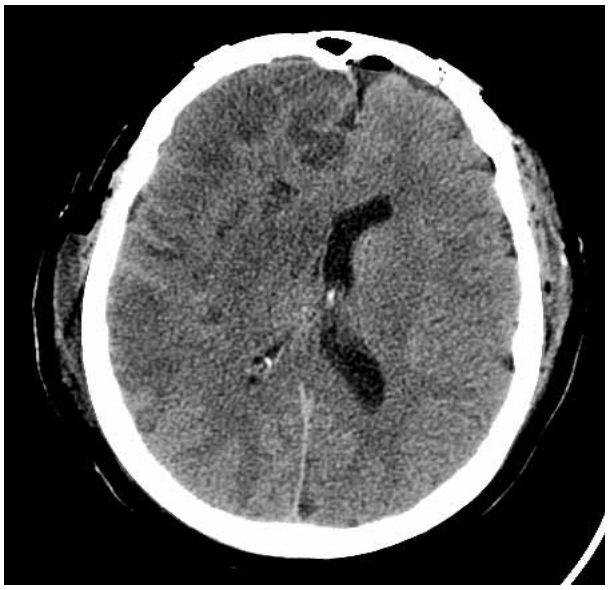

Figure 4: One day post-operative CT head showing near total right MCA and ACA territory infarction.

could not be performed due to the patient's severe claustrophobia.

Physical examination six months post-operatively reveal that the patient has improvement in her left leg strength, while her arm remains non functional; decreased sensation of her left side and left-sided neglect; no useful vision in her right eye; and a temporal field defect in the only seeing left eye (with the loss of vision in the right eye, it is difficult to conclude if she has a bitemporal defect or a homonomous left field defect). Furthermore, some cognitive deficits, especially with maintaining attention, were noted in follow-up in the first year following the infarct. A more recent assessment by a psychiatrist, however, nearly three years after the stroke, shows significant improvement in cognitive function. The patient is orientated, pleasant, cooperative, able to converse in a normal manner with no overt cognitive deficits, and demonstrated fair insight and attention during the exam. She currently lives at home with assistance and her Cushing's disease remains in remission to date.

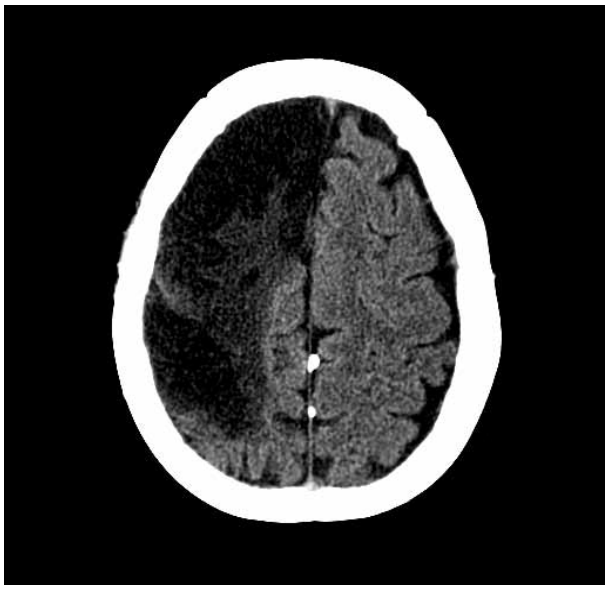

Figure 5: Eight months post-operative non-contrast CT head showing persistent extensive right ACA and MCA infarction with sparing of the posterior right temporal territory. CT scan also demonstrates reduced mass effect and relief of the previous compression of the right lateral ventricle and confirms no midline shift, hydrocephalus, or intracranial hemorrhage.

DISCUSSION

Despite the evidence showcasing the safety and effectiveness of transphenoidal surgery (TSS) as the primary treatment for Cushing's disease (CD) (1,8,14), the pituitary macroadenoma recurred three times in this patient. In a multicentre study by the European Cushing's Disease Survey Group involving 668 patients from 25 institutions over a span of 15 years, the researchers noted a recurrence of Cushing's disease in 12.7% of patients after TSS. The tumour recurred after a mean remission period of 39.3 months (8). Moreover, Benveniste et al. (2005) have shown that repeated TSS is an effective treatment for recurrent or residual mass and has acceptable rates of morbidity and mortality (20). A study that followed 117 Cushing's disease patients for six years found that the remission rate of 85.4% after the first TSS decreased to

28.6% after the second TSS (21). Consequently, we may infer that the remission rate is anticipated to be even lower in our patient after a third TSS and that, perhaps TSS may not be the appropriate first choice of treatment in a patient whose first TSS was not curative. Due to the rarity of Cushing's disease, consensus has not been established as to the best first choice of treatment for recurrent or residual pituitary adenomas; thus, further investigation is warranted.

For patients with CD, alternative or adjuvant treatment options to TSS have been proposed in the literature, including bilaterial adrenalectomy (22,23), medical therapy with adrenostatic drugs (24), radiotherapy (25), and radiosurgery (26). After the second TSS, adjuvant radiotherapy and medical adrenalectomy with Ketoconazole were administered to provide a combined therapeutic regime to our patient. The pituitary tumour was refractory despite this comprehensive treatment approach.

The unique features of this case are that an ACTH-secreting tumour grew to such a large extent that it caused compression of the internal carotid artery (ICA), resulting in cerebral infarction with some pituitary apoplexy. Review of the literature has enabled the generation of several potential explanations for this occurrence. This patient's pituitary adenoma is one of the 12.7% of refractory tumours that recur post-TSS (8). This tumour displayed this refractoriness to treatment since the first TSS and re-grew larger and faster subsequent to each TSS (Figs. 1-2). The tumour extended to the distribution of the cavernous sinus and encased the ICA. Although not obviously radiologically, both intraoperatively and pathologically there were some areas of recent pituitary apoplexy which likely resulted in increased pressure on the carotid artery.

A second explanation worth consideration is that the external beam radiation to the pituitary gland induced the development of vasculopathy in the ICA, which is in close proximity to the pituitary gland, and thus is contained in the radiation field. Reports of radiation-induced vasculopathy date as far back as the 1960s (27,28). Since then, several other cases have surfaced in the literature. In 1993, Marriott et al. documented a case of delayed and focal post-irradiation intracranial vasculopathy resulting in intracranial stenosis. More recently, Penagaricano et al. (2004) make reference to a "syndrome of accelerated cerebral vasculopathy after cerebral radiation therapy" (29). Although conventional instruction in radiation oncology recognizes radiation injury to small vessels and capillaries, damage to large arteries is deemed uncommon. Studies have documented carotid artery radiation injuries following external cervical irradiation where 25% of patients had abnormal phonoangiograms (30). Furthermore, Penagaricano et al. (2004) make the argument that radiation-induced vasculopathy in large arteries, though occuring some time after small vessel injury, may have a greater prevalence than currently presumed (29). The authors also present a case of anterior cerebral artery infarct resulting in a subacute stroke eighteen years following whole brain radiotherapy in a patient with no atherosclerotic risk factors (29). Similarly, Mizokami et al. (1996) report a case of Cushing's disease where the intracranial region exposed to repeated radiotherapy showed more prominent atherosclerosis on angiography compared to the unexposed areas. The pathophysiology is thought to involve large vessel pathology, such as intimal proliferation with or without atheromatosis, thrombosis, and occasional rupture, from targeted radiation at endothelial cells (29).

While the vascular disease that led to the ICA stroke may have been caused by radiotherapy, it may alternately have been the effect of chronic hypercortisolemia. Some studies have found evidence that high blood cortisol levels may be an independent risk factor for atherosclerosis. In one study, a correlation between blood cortisol levels and coronary atherosclerosis was noted, with the most significant association found between plasma cortisol and cholesterol (31). In yet another report, a relationship was identified between salivary cortisol and atherosclerosis of the carotid arteries (32). A review of the current literature (to be published in the journal Current Vascular Pharmacology in 2010) has attempted to elucidate the mechanism by which ACTH and cortisol contribute to atherosclerosis (33). Proposed mechanisms by which these hormones may induce atherogenesis include modulation of vascular endothelial function, recruitment of circulating monocytes to the artery wall and their differentiation into macrophages foam cells, and control of the expression of pro- and anti-inflammatory interleukins. The pathological changes caused by ACTH and cortisol that may lead to stroke include modulating platelet aggregation and thrombus formation (33). Moreover, the case report being presented here provides support to Mizokami et al.'s (1996) proposal that hypercortisolemia may also indirectly contribute to cerebrovascular accidents in patients with Cushing's disease as it accelerates the development of atherosclerotic risk factors such as hypertension, diabetes, dyslipidemia and central obesity (34), which are clinical mani-

festations characteristic of Cushing's disease (17). The patient in this case was also diagnosed with hypertension and diabetes.

Finally, in our case, the etiology of the ICA stroke is most likely multifactorial – a consequence of radiation, hypercortisolemia, a refractory tumour type, and/ or the patient's atherosclerosis risk factors, which include diabetes and hypertension.

Conclusion

This case suggests that pituitary adenomas of the refractory type, hypercortisolemia and/ or pituitary irradiation may be contributors to cerebral infarction in patients with Cushing's disease. It is thus of relevance to the clinician to ensure early diagnosis, close surveillance, and prompt treatment in an effort to prevent cerebrovascular complications in these patients. Also pertinent to the practitioner is the fact that repeated TSS, as was the case in this patient, may not be beneficial; in fact, the radiation may have contributed in part to her ischemic event. Cerebral angiography may be of worthy consideration in patients with refractory pituitary adenomas and atherosclerotic risk factors, especially if they have also received radiotherapy, or if they exhibit focal neurological signs and symptoms. In light of the rarity of Cushing's disease and the limited evidence-based research on this topic, it falls on the clinician to make individualized treatment decisions, taking patient and treatment factors into account, as well as considering the experience and hardships encountered by fellow colleagues in the management of this condition.

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ORIGINAL ARTICLE

Quantifying the increasing use of anti-vascular endothelial growth factor therapy in ophthalmology

Jonathan A. Micieli*, Andrew Micieli

ABSTRACT - *Introduction*: Bevacizumab (Avastin; Genetech Inc., South San Francisco, CA) and ranibizumab (Lucentis, Genetech Inc.) are two anti-Vascular Endothelial Growth Factor (VEGF) agents used in increasing amounts off-label to treat ocular conditions. To date, no study has quantified how far reaching these therapies have been in treating eye disease and compared their off-label use to the number of clinical trials performed. *Method*: A systematic search of Ovid MEDLINE using the keywords bevacizumab and ranibizumab limited to "Case Reports" was used as an index of the number of diseases treated. Each keyword was also limited to "Clinical Trials, All" and "Phase III Clinical Trials" to discern the quality of evidence for these uses.*Results*: Bevacizumab has been utilized for the treatment of 58 different ocular conditions, but only 14 conditions were studied in a trial, and none were part of a phase III clinical trial. Ranibizumab has been used for 17 different eye conditions, with only 6 studied in a trial and only 1 disease, "wet" age-related macular degeneration reported in 4 phase III trials. In the case reports, there were 21 different adverse events ascribed to bevacizumab and 2 to ranibizumab with retinal pigment epithelial tears being the most common. *Conclusion*: Bevacizumab is one of the most far reaching drugs in ophthalmology and even medicine, but it is not yet supported by high quality evidence. The much higher cost of ranibizumab may be responsible for bevacizumab's popularity among eye specialists. Patients should be fully informed about the off-label use of bevacizumab and the associated risks with its use.

KEYWORDS: anti-angiogenic therapy, bevacizumab, ranibizumab, ophthalmology

INTRODUCTION

The revolutionary concept of interfering with the growth of new blood vessels to prevent disease progression began in the field of cancer therapy (1). It was hypothesized that the growth of tumor cells could be significantly diminished if the tumour expression of pro-angiogenic proteins like Vascular Endothelial Growth Factor (VEGF) could be inhibited (2). Bevacizumab (Avastin, Genentech Inc, South San Francisco, California, USA), which is a full-length monoclonal antibody directed against all biologically active forms of VEGF-A, was the first anti-angiogenic drug approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer in conjunction with standard chemotherapy (3). In addition to the treatment of cancer, however, anti-angiogenic therapy has rapidly invaded the field of ophthalmology, particularly in the diseases of the retina, where neovascularization that is spatially and temporally correlated with VEGF expression is a common theme (4). Instead of administering

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these agents intravenously where patients are susceptible to potentially deleterious side effects like hypertension and thromboembolic events (5), the current standard procedure in ophthalmology is an injection directly into the vitreous humor; this has the advantage of localizing the drug to the eye and minimizing any systemic effects (6).

The two most commonly used anti-VEGF drugs in ophthalmology are bevacizumab and the anti-VEGF-A antibody Fab fragment ranibizumab (Lucentis, Genentech Inc, South San Francisco, California, USA), although pegaptanib sodium (Macugen, OCI Pharmaceuticals, Melville, NY), a ribonucleic acid aptamer that binds and inhibits VEGF, is also available (7). Unlike bevacizumab, intravitreal ranibizumab and pegaptanib sodium have been tested in Phase III randomized controlled trials and therefore approved for the treatment of neovascular ("wet") age-related macular degeneration (AMD) (8) , which is the leading cause of irreversible blindness in people over 50 in the developed world (9-11). However, the superior results of ranibizumab compared to pegaptanib sodium in the aforementioned trials have limited the use of the latter in the clinics (12). Compared to bevacizumab, the theoretical advantage of using the smaller ranibizumab fragment is that one can achieve better penetration of all layers of the retina and more effectively target VEGF since this fragment has been engineered to have a higher VEGF affinity (13). However, the relative cost of ranibizumab ($2000 per dose) versus the much cheaper bevacizumab ($50 per dose) has made the latter drug the one of choice for treating other eye diseases off-label when VEGF is implicated, especially when government or insurance coverage is not available (14).

A quick perusal of the ophthalmology literature undoubtedly reveals a plethora of studies utilizing bevacizumab and ranibizumab off-label to treat diseases of the cornea and iris, in addition to those of the retina. For the great majority of the conditions, no randomized controlled trials have been performed to provide high-quality evidence for utilizing these agents, and therefore, many patients are subject to a number of unknown potential risks when receiving these drugs. To date, no study has systematically quantified how far reaching bevacizumab and ranibizumab have been in the field ophthalmology and compared the off-label use to that supported by high quality evidence. The goal of the current study is to quantify how many ocular diseases bevacizumab and ranibizumab have been used for, as represented by published case reports, and to compare this to the number of clinical trials that have been performed. In addition, the number of adverse events reported in case reports will be quantified and discussed in terms of VEGF's critical physiological role in the body.

METHODS

As an index for how far reaching bevacizumab and ranibizumab have been in treating eye diseases, the number of published case reports, clinical trials and phase III clinical trials indexed by Ovid MEDLINE (1996 to August week 1 2009) were utilized. The search strategy, involved using the term *bevacizumab* or *ranibizumab* as a keyword. A search result is obtained if the keyword is found in the original title, abstract, name of substance word, or subject heading word. For each keyword, the search results were limited in three different ways: the first involved limiting the results to "Case Reports" which are defined by MEDLINE as "clinical presentations that may be followed by evaluative studies that eventually lead to a diagnosis" (15). The two other search limitations involved limiting each keyword to "Clinical Trials, All" and "Phase III clinical trials".

According to MEDLINE, a "clinical trial" is defined as "work that is the report of a pre-planned clinical study of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects," and a "Phase III clinical trial" is "work that is a report of a pre-planned, usually controlled, clinical study of the safety and efficacy of diagnostic, therapeutic, or prophylactic drugs, devices, or techniques after phase II trials.

A large enough group of patients is studied and closely monitored by physicians for adverse response to long-term exposure, over a period of about three years in either the United States or a foreign country" (15). All search strategies were limited to the English language.

RESULTS

The results of the search strategies utilizing either *bevacizumab* or *ranibizumab* as keywords are presented in Figure 1. Compared to those for ranibizumab, the reports published with a keyword of bevacizumab were more numerous in the category of case reports (385 vs. 39), all clinical trials (239 vs. 30) and phase III clinical trials (28 vs. 8). From the 385 case reports published for bevacizumab, 229 (59%) described the efficacy, an adverse event, or the characteristics of the drug alone or in combination therapy for an eye condition. Of the remaining 156 papers, 151 were on a topic that did not involve the treatment of the eye such as cancer therapy and 5 were excluded from search since they were retrospective reviews or reports that did not contain sufficient information to discern which eye conditions was treated with bevacizumab. As demonstrated in Table 1, a total 58 different ocular conditions were treated with bevacizumab in the 229 case reports, the most commonly reported condition being wet AMD.

Upon further analysis of the 239 publications classified as a clinical trial for bevacizumab, only 14 different eye conditions represented by 88 publications were studied, the most frequent also being wet AMD (Table 1). There were a total of 144 clinical trial publications on a topic outside the scope of ophthalmology and 7 papers were excluded since they either studied adverse events or other features of bevacizumab treatment for the eye without the mention of the particular conditions being treated. Finally, none of the publications classified as a Phase III Clinical Trial for bevacizumab were on a topic in ophthalmology, as summarized below in Table 1. Consequently, all of the conditions treated were considered off-label.

There were 39 case reports retrieved from the search using ranibizumab as a keyword. From these case reports there were a total of 17 different eye conditions treated with ranibizumab alone or in combination, represented by 36 publications. There was one report that was excluded since it reported the incidence of endophalmitis in an office setting due to anti-VEGF therapy in general. From the publications classified as clinical trials, there were only 6 different eye diseases studied with neovascular AMD being the most numerous. Moreover, wet AMD was the only condition where there existed Phase III Clinical Trials, which have subsequently led to its approval for the treatment of this disease (Table 2). The 4 trials, which have been described in 8 publications from the MEDLINE search, include the ANCHOR [Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD; (16)], MARINA [Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; (17)], FOCUS [(RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety; (18)] and PIER [Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to AMD; (19)] studies.

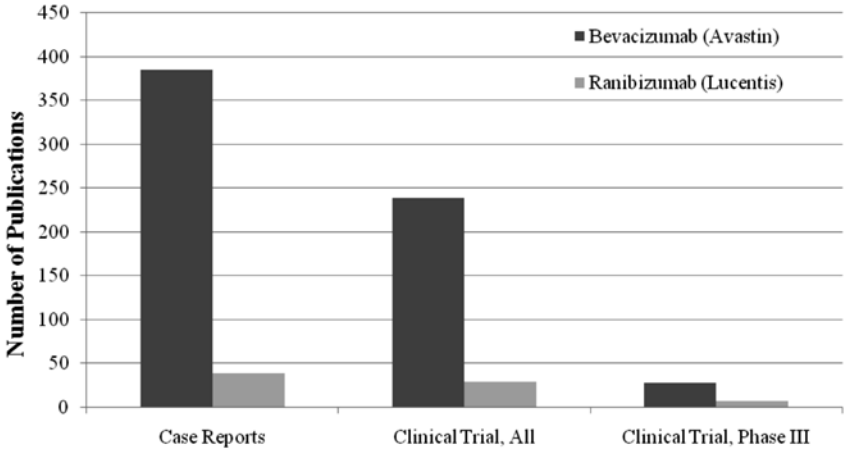

Figure 1: Results of the Ovid MEDLINE search strategy utilizing the keywords bevacizumab or ranibizumab and limited to the category of case reports, all clinical trials or phase III clinical trials.

	Ocular Condition	Case Reports	Clinical Trials	Phase III Trials		Ocular Condition	Case Reports	Clinical Trials	Phase III Trials
1	Neovascular AMD	**51**	**32**	**none**	31	Proliferative sickle retinopathy	**2**	**none**	**none**
2	NV glaucoma	**21**	**2**	**none**	32	Central serous retinopathy	**2**	**none**	**none**
3	Proliferative DR	**16**	**8**	**none**	33	Presumed ocular histoplamosis (CNV)	**2**	**none**	**none**
4	Corneal neovascularization	**11**	**2**	**none**	34	ME due to occlusive vasculitis	**2**	**none**	**none**
5	Angiod Streaks (CNV)	**10**	**1**	**none**	35	Punctate inner choriodopathy	**2**	**none**	**none**
6	BRVO	**8**	**11**	**none**	36	Radiation Retinopathy	**1**	**2**	**none**
7	CRVO	**8**	**7**	**none**	37	Familial exudative vitreoretinopathy	**1**	**none**	**none**
8	Pathological Myopia (CNV)	**8**	**6**	**none**	38	CRAO	**1**	**none**	**none**
9	ROP	**5**	**none**	**none**	39	Ocular ischemic syndrome	**1**	**none**	**none**
10	Inflammatory CNV	**5**	**2**	**none**	40	Toxoplasmosis (CNV)	**1**	**none**	**none**
11	Peripapillary CNV	**5**	**none**	**none**	41	Vogt-Koyanagi Horadu syndrome (CNV)	**1**	**none**	**none**
12	Retinal Angiomatous Proliferation (CNV)	**5**	**1**	**none**	42	ME due to optic disc vasculitis	**1**	**none**	**none**
13	Iris NV	**4**	**none**	**none**	43	Post-capsule vessels (after cataract surg)	**1**	**none**	**none**
14	Pseudophakic cystoid ME	**4**	**2**	**none**	44	Gronblod-Stranberg syndrome (CNV)	**1**	**none**	**none**
15	Coats disease	**4**	**none**	**none**	45	Vasoproliferative tumour	**1**	**none**	**none**
16	Juxtafoveal telangiectasia	**4**	**none**	**none**	46	PRV due to polycythemia rubra vera	**1**	**none**	**none**
17	Macular telangiectasia	**3**	**none**	**none**	47	Pterygium	**1**	**none**	**none**
18	Corneal transplant	**3**	**none**	**none**	48	Cystoid ME in retinitis pigmentosa	**1**	**none**	**none**
19	Choroidal metastases	**3**	**none**	**none**	49	Cystoid ME in Behcet disease	**1**	**none**	**none**
20	Choroid Osteoma (CNV)	**3**	**none**	**none**	50	Sorsby fundus dystrophy	**1**	**none**	**none**
21	Perifoveal telangiectasia	**3**	**none**	**none**	51	WNV choroidretinitis (CNV)	**1**	**none**	**none**
22	Polypoidal choroidal vasculopathy	**3**	**none**	**none**	52	Bleb hyperemia (post-trabeculectomy)	**1**	**none**	**none**
23	Idiopathic CNV	**2**	**1**	**none**	53	Gyrate atrophy	**1**	**none**	**none**
24	Diabetic macular edema	**2**	**12**	**none**	54	Nonarteritic Anterior Ischemic Optic Neuropathy	**1**	**none**	**none**
25	Multifocal choroiditis	**2**	**none**	**none**	55	Radiation Optic Neuropathy	**1**	**none**	**none**
26	Juxtapapillilary retinal capillary hemangioma	**2**	**none**	**none**	56	Sponatneous cystoid ME	**1**	**none**	**none**
27	Glaucoma filtering surgery	**2**	**none**	**none**	57	Pseudotumor cerebri (CNV)	**1**	**none**	**none**
28	Eales disease	**2**	**none**	**none**	58	Birdshot chorioretinopathy	**1**	**none**	**none**
29	Adult-onset vitelliform dystrophy	**2**	**none**	**none**					
30	Best disease	**2**	**none**	**none**					

Table 1: The number of ocular conditions treated with bevacizumab (Avastin) indexed by the number of case reports published. AMD = age-related macular degeneration; NV= neovascular; DR = diabetic retinopathy; CNV = choroidal neovascularization; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; ROP = retinopathy of prematurity; ME = macular edema; PRV = peripheral retinal vascularization. References are provided in parentheses for those with 5 or less reports.

	Ocular Condition	Case Reports (references)	All Clinical Trials (references)	Phase III Trials (references)
1	Neovascular AMD	**20**	**20**	**4**
2	Retinal Angiomatous Proliferation (CNV)	**2**	**1**	**none**
3	CRVO	**none**	**3**	**none**
4	BRVO	**none**	**1**	**none**
5	Angiod Streaks (CNV)	**1**	**none**	**none**
6	Diabetic macular edema	**1**	**1**	**none**
7	Diabetic macular traction	**1**	**none**	**none**
8	Idiopathic CNV	**1**	**none**	**none**
9	Macular Telangiactasia	**1**	**none**	**none**
10	Multifocal choroiditis	**1**	**none**	**none**
11	Multiple Evanescent White Dot Syndrome	**1**	**none**	**none**
12	NV Glaucoma	**1**	**none**	**none**
13	Peripapillary CNV	**1**	**none**	**none**
14	Pterygium	**1**	**none**	**none**
15	Retinal Capillary Hemangioblastoma	**1**	**none**	**none**
16	Stargardt's disease (CNV)	**1**	**none**	**none**
17	Toxoplasmosis (CNV)	**1**	**none**	**none**
18	Vitelliform macular dystrophy (CNV)	**1**	**none**	**none**
19	Myopic CNV	**none**	**1**	**none**

Table 2. The number of ocular conditions that have been treated with Lucentis (Ranibizumab) and published as a case report or studied in a clinical trial. AMD = age-related macular degeneration; NV= neovascular; CNV = choroidal neovascularization; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion. References are provided in parentheses for those with 5 or less reports.

The number of adverse events published in a case report after treatment with bevacizumab totaled 20. The most frequently identified side effect was tears of the retinal pigment epithelium (RPE) in 14 papers (20), followed by endophalmitis in 6 papers (21), progression of ischemia (22) and retinal detachment (RD) with a macular hole (23) reported in 2 papers each. In addition, there was one case report describing each of the following adverse events: retinal circulatory disturbances (24), progression of a RD (25), herpetic epithelial keratitis (26), papulopustular rash (27), rebound macular edema (28), sixth nerve palsy (29), acute glaucoma (30), sustained increase in intraocular pressure (IOP) (31), visual hallucination (32), sympathetic ophthalmia following vitrectomy for endophalmitis (33), anterior uveitis (34), acute visual acuity loss (35), large subretinal hemorrhage (36), and anterior ischemic optic neuropathy (37). Perhaps the most interesting case was vitritis in the contralateral, untreated eye (38), which suggests that bevacizumab has the potential to reach the systemic circulation and penetrate many body compartments. For ranibizumab, there were 7 case reports suggesting an adverse reaction from the drug: 6 described RPE tears (39) and one described persistent ocular hypertension (40).

DISCUSSION

Despite the fact that ranibizumab is the only anti-VEGF therapy approved by licensing bodies for ocular use, bevacizumab is by far the agent with the widest scope in ophthalmology. In the current study, we identified 58 different ocular conditions that were treated off-label compared to only 19 with ranibizumab. There are a few reasons for this occurrence that include the timing of introduction of bevacizumab and ranibizumab and the relative costs of the two drugs. In mid-2005, retina specialists had two therapies that had been proven effective and safe for neovascular AMD by randomized, double masked-trials: photodynamic therapy (PDT) and pegaptanib sodium (Macugen), which is an anti-VEGF aptamer (14). Just after the results of the ranibizumab trials were being reported that same year, but before the FDA approved it for neovascular AMD in June 2006, retina specialists began using bevacizumab because it was believed

that its similar structure to ranibizumab would confer similar results. Indeed, the American Society of Retinal Surgeons survey on bevacizumab use found that 84% of retinal specialists preferred the off-label Avastin over PDT or Macugen even though the latter drug was supported by level one scientific evidence (41). Consequently, retinal physicians began to gain confidence with the effectiveness and safety of bevacizumab despite the higher quality evidence that emerged for ranibizumab. The compounding and often important factor is the relative cost of the two drugs. Many provinces including Ontario cover ranibizumab for those with neovascular AMD over the age of 65. However, some AMD patients, who have not yet reached the age of 65 and do not have the finances nor the insurance, are faced with a dilemma of whether to suffer the financial consequences of ranibizumab injections or receive bevacizumab which is considerable cheaper ($2000 vs $50, respectively) and potentially just as effective.

The familiarity with bevacizumab has penetrated ophthalmological diseases beyond neovascular AMD and has become the most versatile agent in this area of specialization. Despite any randomized, controlled Phase III trials, bevacizumab has become included in the standard of care for many conditions including proliferative diabetic retinopathy and is administered concomitantly with laser photocoagulation at certain sessions (42). Moreover, conditions like neovascular glaucoma, which develop secondary to ischemic retinal vein occlusions or diabetic retinopathy, can be managed much more effectively with bevacizumab than with pressure lowering drops alone (43). In addition, diseases like retinopathy of prematurity, which are currently managed with destructive procedures like cryotherapy or laser photocoagulation and often accompanied by poor outcomes in aggressive cases, are being considered for treatment with bevacizumab since VEGF-induced proliferation is central to the disease process (44). However, with no large trials to adequately evaluate its safety, especially in newborns, caution must be taken as bevacizumab continues to grow in popularity. The current study did not include an analysis of pegaptanib sodium to accompany the results of bevaciumab and ranibizumab. The primary reason for this is that this more selective agent that only inhibits the $VEGF_{165}$ isoform has demonstrated inferior results when compared to ranibizumab in phase III clinical trials for “wet” AMD and has consequently assumed less importance than the non-selective VEGF agents at the current time (7, 12, 17). In the future, however, pegaptanib sodium may attain a more prominent role as a second line, maintenance therapy that can be employed after a sequence of ranibizumab and bevacizumab injections have been given (45). The rationale for this use is that it can preserve the beneficial physiological actions of some VEGF isoforms which may be needed over a long period of time while inhibiting the dominant $VEGF_{165}$ subtype and consequently reducing the chance of developing a new neovascular lesion. In addition, the current study was limited in that the case reports used as an index of the use of ranibizumab and bevacizumab may not be completely indicative of their use in ophthalmology clinics. These reports may only reflect current hypotheses and investigational uses that are still awaiting further clinical trials before they become more widely accepted in the future. Nonetheless, it may be some time before clinical trials are organized for many less common diseases prompting some clinicians who have not yet adopted the drug to begin introducing it at increasing amounts in the future.

The increasing off-label use of bevacizumab and ranibizumab beyond the numerous conditions identified here has the potential to also lead to an increasing number of adverse reactions to the drugs. VEGF has a number of critical roles in the vasculature including maintaining the health of the retinal pigment epithelium and the microcirculation,(46) and serving as a critical factor in the adaptive response to ischemic injury in which the elderly, who are often the population treated with these agents, are at greater risk. In response to ischemic injury, VEGF serves as a neuroprotectant directly by influencing anti-apoptotic gene expression and indirectly by functioning as a vasodilator and increasing blood flow to the area (47). Its latter function is a result of its ability to alter the distribution of the tight junction protein occludin in endothelial cells (48, 49) and upregulate nitric oxide in arterioles and venules (50). Indeed, a recent study evaluating treatment of naïve patients with neovascular AMD noted significant retinal arteriolar narrowing after monthly intravitreal injections of ranibizumab (51). The

concern for systemic effects, however, should be greater with bevacizumab than ranibizumab, since it can utilize endogenous immunoglobulin transport systems like the FcRn or neo-natal receptor, which are expressed at high levels in the eye and used to transport antibodies to help them escape catabolism (52). In fact, pharmacokinetic studies in rabbits have found persistent levels of bevacizumab in the serum that do not drop below 1ug/mL until 30 days post-injection and nanogram levels in the contralateral eye after intravitreal injection of 1.25mg (53). Considering that normal serum VEGF levels are on the order of 100 pg/mL (54), an excess of free bevacizumab in the serum could neutralize the protective functions of VEGF and have clinical manifestations. Could we therefore see more systemic thromboembolic adverse events in the future as bevacizumab grows in importance? Even large clinical trials enrolling a few thousand patients may not have the statistical power yet to detect low rates of adverse events. One primary concern that is currently under investigation is whether long-term treatment with ranibizumab for wet AMD can accelerate a transition to geographic atrophy, a dry debilitating end-stage of AMD, since VEGF helps maintain the health of the normal retinal neurons and the retinal pigment epithelium. (55). Consequently, further large scale studies and effective mechanisms that allow for reporting of potential adverse events should be put in place to better identify relationships between intravitreal anti-VEGF therapy and adverse consequences.

CONCLUSION

Bevacizumab is a far-reaching anti-VEGF agent used in ophthalmology, being described for use in 58 different conditions. The smaller ranibizumab fragment is the only anti-VEGF currently approved for ocular use in neovascular AMD and has been described for use in 18 other eye diseases. As the use of bevacizumab and ranibizumab increases in our aging population, the potential for more adverse events with these agents will inevitably grow beyond the 20 published case reports of adverse events to date. Caution should be used by all treating physicians who opt to use these agents in their practice and patients should be fully informed regarding their use and be made aware of the off-label nature of these therapies.

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ORIGINAL ARTICLE

Maternal Hemoglobin Concentration and Pregnancy Outcome: A Study of the Effects of Elevation in El Alto, Bolivia

Elise M. Laflamme*

ABSTRACT: Iron-deficiency anemia is often under-diagnosed in developing countries, specifically in pregnant populations in regions of high altitude. Hemoglobin levels are not consistently adjusted for elevation, and therefore many anemic patients are left undiagnosed. The purpose of this study was to incorporate current parameters for diagnosing anemia in pregnancy at high altitudes, and to evaluate the effects of appropriately adjusted hemoglobin concentrations on pregnancy outcome. A few studies have examined the effect of elevation on hemoglobin status, and other studies have considered the effects of anemia of pregnancy; however, there is a lack of data demonstrating that altitude-adjusted hemoglobin levels accurately predict pregnancy outcome. Using the Student t-Test, multiple linear regression, and ANOVA statistical analyses, various factors of pregnancy outcome were compared between anemic and non-anemic groups, as defined by hemoglobin cut-off levels adjusted for trimester of pregnancy and altitude. When appropriate adjustments were used, maternal anemia was associated with lower infant Apgar scores at both one minute and five minutes after birth, as well as complication of labor, lower gestational age at birth, and higher parity. This study demonstrates the importance of altitude and trimester specific adjustments to maternal hemoglobin levels in order to accurately diagnose anemia in pregnancy. In addition, a clear correlation is seen between maternal hemoglobin level and pregnancy outcome.

KEYWORDS: Iron-Deficiency Anemia, Pregnancy, Bolivia, Elevation, Altitude, Hemoglobin

INTRODUCTION

Iron-deficiency anemia is a health problem that often goes untreated, especially in pregnant women living in developing countries, where it can be most dangerous. The World Health Organization (WHO) estimates that an average of 56% of pregnant women in developing countries are anemic.1 This percentage ranges from 35-75% in specific areas, and is much higher than the 18% of pregnant women diagnosed with anemia in developed countries (1). Iron deficiency during pregnancy is thought to be caused by combination of factors such as previously decreased iron supply, the iron requirements of the growing fetus, and expansion of maternal plasma volume (2). While plasma volume and red blood cell mass are both known to expand during pregnancy, plasma volume grows to a greater extent, therefore diluting the maternal hemoglobin concentration (Hb) (3). It is necessary to take this into consideration when diagnosing anemia in pregnant women. Effective diagnosis has been achieved by laboratory tests of hemoglobin and hematocrit (Hct) levels. However, it is also necessary to identify precise cut-offs for anemia ac-

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cording to age and current trimester of pregnancy. Research has found that Hb and Hct concentrations typically decrease during the first trimester, reach the lowest levels at the end of the second trimester, and increase again during the third trimester of pregnancy (4). The Center for Disease Control (CDC) has used this research to establish trimester-specific Hb concentration adjustments for diagnosing anemia in pregnancy (Table 1). Hemoglobin adjustments for an unknown trimester dating have been developed by the WHO (5).

Hemoglobin levels have also been known to vary in response to altitude. Elevations of over 1000 meters increase patient Hb levels (3). This is known as an adaptation response to the lower partial pressure of oxygen, which causes reduced oxygen concentration in the blood. The body responds to this change by increasing Hb concentration in order to ensure that oxygen transport is sufficient for tissues requirements (3). This Hb increase can ultimately mask anemia if it is not carefully considered (6). In order to determine Hb concentration cut-off levels for anemia at varying altitudes, the CDC Pediatric Nutrition Surveillance System2 has used data from a study of children with little or no iron deficiency. Using this data, they developed a curve of Hb concentrations as altitude changed, demonstrating the following association between altitude and Hb:

Hb = -.32 * (altitude in meters *0.0033) + 0.22 * (altitude in meters * 0.0033)

Although the Hb adjustment curve developed by the CDC is currently used internationally, it was not developed with the specificity for use in pregnancy. For this reason, studies that confirm or refute the usefulness of this adjustment curve in the pregnant population are necessary.

In addition, it is evident that the effects of maternal anemia on the outcome of pregnancy are not completely understood (1). A U-shaped association has been found between the maternal Hb level and the birth weight of the infant. High Hb concentration has been associated with inadequate plasma volume expansion, often leading to a lower birth weight or other adverse pregnancy outcomes (7-8). Low birth weight can also be associated with maternal anemia due to preterm labor induced by low Hb levels (1,9). Data shows that anemia early in pregnancy is associated with increased risk of preterm premature rupture of membranes, while anemia later in pregnancy is associated with spontaneous premature labor (9). Furthermore, it is worthwhile to note the many short-term and long-term outcomes associated with preterm infants born with a low birth weight, such as cerebral palsy, blindness, deafness, hydrocephaly, diabetes, hypertension, and heart disease (10). Finally, there is a positive correlation between Apgar scores and maternal Hb concentrations, as well as treatment with iron supplement (11-12). Multiple pregnancies and low socioeconomic class are additional risk indicators for iron-deficiency anemia (8). In order to improve prenatal health, additional research is necessary to confirm previous associations. It is crucial that these associations between maternal anemia and pregnancy outcome be explored under appropriate adjustments to hemoglobin cut-off levels in areas of high elevation.

Trimester of Pregnancy	Hemoglobin Adjustment (g/dL)
First	-1.0 g/dL
Second	-1.5 g/dL
Third	-1.0 g/dL
Unknown Trimester	-1.0 g/dL

Table 1: Hemoglobin adjustments for pregnant women at sea level

Although most cases of anemia in pregnancy are caused by iron deficiency (13) other types of anemia must also be considered in the diagnosis. These include pure red cell aplasia, aplastic anemia, paroxysomal nocturnal hemoglobulinemia, and myelodysplastic syndrome (13). The classification of various types of anemia is based upon origin and morphology of red blood cells. Origin is classified based on bleeding, increasing destruction of blood cells, and decreased production of cells. Morphology is classified by cell size, shape and color. Based on these classifications, anemias are placed in categories of macrocytic or nomochromic anemias (B12 deficiency or folate deficiency), microcyic of hypochromic anemias (iron deficiency, sideroblastic, or thalassemia anemia), or normocytic or normochromic anemias (aplastic, hemolytic, chronic disease, or sickle cell) (14).

There are many women with iron-deficiency anemia that are not aware of their condition. Iron-deficiency ranges from iron depletion, which causes no physiological harm to the patient, to iron-deficiency anemia, which can cause multiple organ failure syndrome, impaired cognitive performance, immunosuppression, physical weakness, impaired gastrointestinal function, and altered hormone production and metabolism (5). Iron-deficiency anemia can be diagnosed accurately if the Hb concentration of the patient rises after routine iron supple-

mentation (8). Although iron-deficiency anemia is the most common type of anemia diagnosed, the various other types of anemia must also be considered when diagnosing a patient with iron-deficiency anemia.

Iron supplementation during pregnancy has been implicated around the world in hopes of increasing the iron supply of anemic patients. Studies demonstrate that these supplements can increase infant birth weight (15-16). A Nigerian study on iron supplementation during pregnancy found that iron supplements could also increase Apgar scores of infants (1). Other studies show that supplements do not consistently decrease the incidence of iron-deficiency anemia in women that have entered pregnancy with low Hb levels and low iron stores. More specifically, some research illustrates that anemia in pregnancy can only be reduced if supplementation is initiated before conception (17). Regardless of varying study outcomes, many share the opinion that we should practice routine iron supplementation during pregnancy, most importantly to anemic pregnant women (1).

The purpose of this study was to evaluate the effect of trimester and altitude-adjusted Hb levels on and pregnancy outcome. Although the effects of altitude on Hb concentration is established, many patients in developing countries remain undiagnosed with anemia due to failure to apply these Hb adjustments. In this study we provide data that demonstrates that the application of altitude-specific Hb adjustments for anemia is useful in the prediction of pregnancy outcome. Additionally, we determine which specific aspects of pregnancy outcome are most affected by maternal Hb concentration in the population of pregnant women in El Alto, Bolivia, when Hb is appropriately adjusted for the effects of elevation.

METHODS

Study Cohort:

This study was carried out in May 2006 in El Alto, Bolivia, at the Los Andes Hospital. This institution is a small hospital which services mothers and children. El Alto is a growing city of over 500,000 people, found at an altitude of 4018 meters above sea-level (18). The the study was approved by Northeastern University's Director of Research Integrity. Review by the FDA's Institutional Review Board was waived by Northeastern, as work was done under the direction of Dra. Cecilia Uribe de Chavez, the local Medical Director of Child and Family Health International. Consent to review patient charts was given by Dra. Uribe. Subjects were randomly chosen as they gave birth in the hospital, and charts were reviewed after verbal consent by patients. Only subjects with complete data were included in the study.

Ninety-eight patient charts were reviewed by a Spanish interviewer. Patient information was transcribed to a data collection sheet, which included patient parity, weight, height, hemoglobin and hematocrit levels, infant birth weight, length, head circumference, gestational age, Apgar scores, and any other complications in pregnancy. Gestational age was quantified as the number of weeks between the patients' last recalled menstrual period and the day of delivery.

Hemoglobin measurement:

Hemoglobin levels were categorized as "anemic" and "non-anemic," according to The World Health Organization's accepted values to define anemia, along with the adjustments provided by the CDC to determine anemia during pregnancy. Averages of pregnancy number (parity), gestational age, birth weight, birth length, head circumference and Apgar scores at 1 and 5 minutes were calculated for both "anemic" and "non-anemic" patients. These averages were analyzed for statistically significant relationships with Hb levels using the t-TEST in Microsoft Excel Data Analysis Toolpack.

Hemoglobin concentrations were sorted into four categories of 1.99 g/dL per category, ranging from 7.00 g/dL to 14.99 g/dL. Categories were labeled based on the CDC's trimester-specific cut-off level for anemia in pregnancy as High-Normal (13.00-14.99 g/dL), Normal (11.00-12.99 g/dL), Mild (9.00-10.99 g/dL), Moderate (7.00-8.99 g/dL), and Severe anemia (<7.00 g/dL). Hb levels above 14.99 g/dL and below 7.00 g/dL were considered extraneous and unusable in our study due to the few data points found in these ranges. Using this data in our analysis would have caused unequal group sizes. Means of collected data for pregnancy outcome factors were calculated for each category.

Hemoglobin adjustment was calculated by subtracting the adjustment value from the measured Hb concentration at the relevant altitude, to the nearest 500 meters, in order to obtain the comparative sea-level value. The increase in Hb concentration due to elevation and lower atmospheric partial pressure is often misinterpreted as a sign of sufficient iron status, while a patient from a high-altitude area may actually have iron-deficiency anemia. It is important to determine whether women with apparently normal Hb levels at high elevation are actually anemic and whether or not these seem-

Variable	n	Mean ± SD	Median
Age, *years*	98	27.20 ± 6.90	26.0
Height, *cm*	74	148.40 ± 6.20	148.0
Weight, *kg*	80	56.00 ± 9.80	55.1
Weight at Birth, *kg*	65	65.10 ± 9.60	64.5
BMI, *kg/m²*	51	29.50 ± 4.40	30.1
Maternal Hb, *g/dL*	79	12.97 ± 2.07	13.4
Maternal Hb (altitude-adjusted), *g/dL*	79	12.61 ± 2.08	13.0
Infant Gestational Age, *weeks*	94	38.50 ± 2.10	39.0
Infant Birth Weight, *g*	97	3,200 ± 500	3,300
Infant Birth Length, *cm*	95	47.76 ± 4.30	49.0
Infant Head Circumference, *cm*	95	37.90 ± 31.90	34.8
Apgar Score, *1 min*	95	7.40 ± 1.30	8.0
Apgar Score, *5 min*	95	9.00 ± 1.40	9.0
Parity	75	1.80 ± 1.90	1.0

Table 2: Characteristics of the study population, El Alto, Bolivia

ingly normal Hb concentrations, after adjusting for elevation, actually serve as a risk factor for poor pregnancy outcome. Based on previous research and suggested Hb adjustment values (4), we subtracted 0.34 g/dL from all patients' Hb concentrations in order to consider the effects of altitude.

In this study, anemia is defined as a Hb level lower than the "Normal" (<11.0 g/dL) Hb level at the defined altitude. Hb concentrations during pregnancy are generally lower due to the maternal plasma expansion, along with the growing fetus's use of the maternal iron stores (2).

For these reasons, data in this study was used only if maternal Hb concentration was analyzed before the end of the first trimester of pregnancy. Studies have concluded that Hb cutoff levels to define anemia in non-pregnant females above the age of fifteen should be 12.0 g/dL (3). Furthermore, the CDC has developed trimester-specific cutoff level adjustments for pregnant women. These can be calculated by trimester by subtracting values as in Table 1.4 The blood tests used to determine patient Hb levels in this study were run during the first trimester of pregnancy, and therefore the cutoff level used for identifying anemia was 11.0 g/dL.

Statistical analysis:

Multiple linear regression analysis was used to determine the effect of Hb levels on factors of pregnancy outcome, considering any confounding variables that may influence both Hb levels and outcomes. Pregnancy outcome factors analyzed by this regression included gestation age, Apgar scores at 1 and 5 minutes following birth, and birth weight of infant. Parity was also examined as a possible determinant of Hb concentration using this analysis. Regression was applied using Microsoft Excel Data Analysis Toolpack.

Using SPSS 14.0.1 for Windows, ANOVA (ANalysis Of VAriance between groups) was applied to determine the statistically significant difference between the means of the four categories. Further post hoc Tukey honest significant difference (HSD) analysis ($P < 0.05$) was applied to all data analyzed in the ANOVA.

RESULTS

Study cohort:

This study included 98 women (Table 2). Descriptive variables of maternal health and variables of pregnancy outcome were analyzed from the available data. The average age of the women evaluated was 27.2 years, while the median age was 26.0 years. The majority of the women were from El Alto (82), while the others were from the nearby areas of La Paz, Polochoco, Alto Lima, Challahuyo, Guayuyo, Yuayayo, Achacadi, Puerto de Gui Gui, and Brosil.

The average hemoglobin concentration of the subjects was 12.965 g/dL, which was adjusted to 12.609 g/dL using the Center for Disease Control

	ANEMIC	NON-ANEMIC	P VALUE
Hb, *g/dL*	9.31	13.7	$1.16e^{-08}$
Hb (altitude-adjusted), *g/dL*	8.97	13.4	$1.19e^{-09}$
Gestation Length, *weeks*	37.1	38.9	0.059
Birth Weight, *g*	$3.10e^{03}$	$3.30\ e^{03}$	0.213
Birth Length, *cm*	47.8	47.5	0.431
Head Circumference, *cm*	34.2	39.5	0.137
Apgar, *1 minute*	5.90	7.60	0.006
Apgar, *5 minute*	7.80	9.20	0.039
Parity	4.10	1.50	0.010
Birth Complications	64.3% with complications	15.4% with complications	0.002

Table 3: Comparison of means between pregnancy outcome in anemic and non-anemic pregnant women (n = 80)

and Prevention's anemia criteria and altitude adjustment (19).

Hemoglobin levels:

Based on the altitude and pregnancy-adjusted Hb concentrations, 14 of the 80 pregnant women were defined as anemic (17.5%). The means of various factors of pregnancy outcome between anemic and non-anemic groups were compared (Table 3) and statistically significant differences were assessed using Student's t-TEST. Maternal anemia was associated with lower infant Apgar scores at both 1 and 5 minutes after birth. The stronger relationship was observed in the effects of anemia on low Apgar scores at 1 (P = 0.006), versus at 5 minutes (P = 0.039).

Birth complications:

Birth complications were more prevalent in anemic women than in non-anemic women. In this study, any major deviation from normal, healthy labor was considered a "complication." A patient was considered positive for birth complications if she underwent an emergency cesarean section, experienced preeclampsia, if the infant needed oxygen through a facemask, or was stillborn. While 64.3% of anemic subjects experienced some type of birth complications, only 15.4% of non-anemic subjects faced these problems. Women who experienced birth complications were assigned the categorical value of "1," and women with no complications were assigned a value of "0." These categorical values represent the possible outcomes, while the anemic and non-anemic categories represent the variables. A t-TEST was run with this data, and showed a strong correlation between maternal anemia and complications in birth (P = 0.002).

Parity, gestational age, and birth weight:

Higher parity was associated with anemia, with 4.1 previous pregnancies in anemic women compared to 1.5 previous pregnancies in non-anemic women (P = 0.010). Although the average gestational age of infants born to anemic women was nearly two weeks less than that of infants born to non-anemic women, this difference failed to reach statistical significance (P = 0.059). Average birth weight of infants of anemic patients was 210 g less than the average birth weight of those of non-anemic patients, however, no statistical significance was observed (P = 0.213).

Pregnancy outcome:

Complete data for both Hb concentrations and all evaluated pregnancy outcome factors were available for a total of 56 woman-infant pairs. Multiple linear regression was used to assess the relationship between maternal Hb levels and the various predictors of pregnancy outcome. All measured outcomes of pregnancy were included in the regression model. Using this multivariate regression, there was a statistically significant association between Hb level and gestation age (P = 0.0284), the Apgar score at 1 minute (P = 0.00039) and at 5 minutes (P = 0.018), as well as parity (P = 0.00082). This data may suggest that women with higher parity are more likely to become anemic, or that women with multiple births did not have sufficient time to recover their hemoglobin stores following their previous pregnancies. Additional studies may be beneficial in determining the exact association, and the supporting physiology, between parity and consequent hemoglobin levels.

Patient stratification based on hemoglobin concentration:

Subjects were divided into six groups based on their maternal Hb level (Table 4). The means of various pregnancy outcomes were calculated for each Hb category. In further analysis, only data from subjects with Hb concentrations between 7.00 g/dL and 14.99 g/dL were used, as there were

Hb, *g/dL*	**n**	**MEANS OF PREGNANCY OUTCOME FACTORS**					
		Hb, *g/dL*	**Birth Weight, *g***	**Apgar, *1 min***	**Apgar, *5 min***	**Gestation, *weeks***	**Parity**
7.00-8.99	7	8.25	2,950	4.750	6.50	37.60	3.65
9.00-10.99	6	10.26	3,006	6.875	8.75	36.50	5.75
11.00-12.99	20	11.97	3,231	7.357	9.05	38.40	1.85
13.00-14.99	41	13.99	3,208	7.761	9.35	39.10	1.27

Table 4: Categorical Hb levels and associated means of pregnancy outcome factors (n=74)

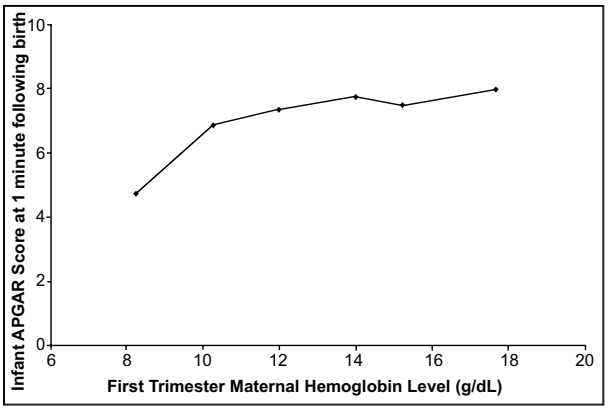

Figure 1a: Effects of first trimester materinal hemoglobin level (g/dl) on infant health, as measured by APGAR socre at 1 minute following birth (n=74). All measurements taken in El Ato, Bolivia, elevation 4018 meters above sea level.

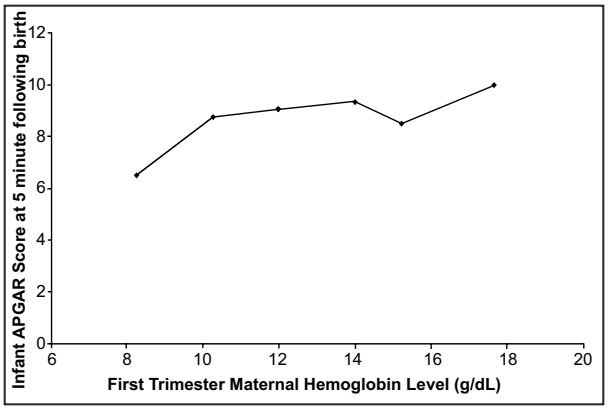

Figure 1b: Effects of first trimester materinal hemoglobin level (g/dl) on infant health, as measured by APGAR socre at 5 minute following birth (n=74). All measurements taken in El Ato, Bolivia, elevation 4018 meters above sea level.

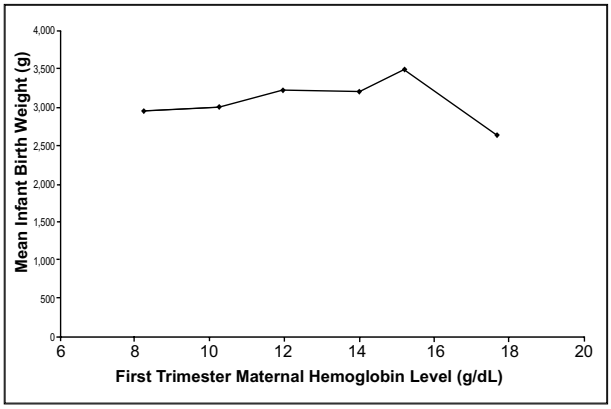

Figure 2: Effects of first trimester materinal hemoglobin level (g/dl) on infant health, as measured by mean infant birth weight (g) (n=74). All measurements taken in El Ato, Bolivia, elevation 4018 meters above sea level.

not enough data in the upper categories to make statistically significant conclusions.

When mean Apgar scores recorded at 1 minute were plotted against the Hb groups, Apgar scores appear to increase gradually from low to high maternal Hb levels (Figure 1a). At lower Hb levels, Apgar score increases significantly as maternal Hb levels increase. At higher maternal Hb levels, Apgar scores tend to increase less drastically and the trend curve levels off. When plotting Hb groups against Apgar scores at 5 minutes after birth, a similar trend is observed (Figure 1b). However, the curve formed from this data includes a point that falls off the apparent trend line (at Hb concentrations of 15.21 g/dL.)

Average birth weight of the infants also showed a slight increase as Hb concentrations increased (Figure 2). The point on this plot referring to mean Hb of 17.66 g/dL demonstrates that the U-shaped association between Hb concentration and birth weight (Figure 2) may be present weakly within our data.

ANOVA analysis of pregnancy outcomes and Hb levels:

ANOVA analysis was used to evaluate these observed trends. Subjects with Hb concentrations below 7.00 g/dL and above 14.99 g/dL were not included in the ANOVA analysis. The analysis confirmed that correlations between differences in increasing Hb concentrations and gestation length were statistically significant ($P = 0.007$). When this method was used to evaluate the relationship between increasing Hb levels and infant birth weight, no statistically significant differences were present ($P = 0.458$). However, statistical significance was identified in the relationship between increasing Hb levels and infant Apgar scores at 1 minute ($P = 0.000$), and at 5 minutes ($P = 0.002$), and parity ($P = 0.000$).

Post hoc Tukey HSD analysis of pregnancy outcomes and Hb levels:

Using the same data and same four Hb groups (7.00-8.99 g/dL, 9.00-10.99 g/dL, 11.00-12.99 g/dL, and 13.00-14.99 g/dL), the ANOVA analysis was further developed with an post hoc Tukey HSD analysis. When examining gestation length as a dependent variable, subjects with mild anemia (Hb 9.00-10.99 g/dL) had significantly lower gestational lengths ($P < 0.05$) than groups those of the Normal (11.00-12.99 g/dL) and High-Normal (13.00 – 14.99 g/dL) groups, which are statistically equal to the Moderate anemia group (7.00-8.99 g/dL).

In comparing Hb groups with respect to the infants' Apgar scores at 1 minute following birth, the Moderate anemia group had lower scores than the Normal and High-Normal groups, which were statistically equal to the Mild Anemia group. When Tukey's HSD analysis was repeated with Apgar scores at 5 minutes following birth, the same relationships were observed as in Apgar scores at 1 minute. Finally, parity in the Mild and Moderate anemia subjects was found to be significantly greater than in the Normal and High-Normal group subjects.

DISCUSSION

This study demonstrates the importance of using Hb cut-off levels specific to elevation in the diagnosis of iron-deficiency anemia. As illustrated in the data, 17.5% of the pregnant study population from El Alto can be diagnosed with maternal anemia using diagnostic cut-off levels adjusted for elevation. Without using these adjusted Hb levels, only 11.39% of the study population would be diagnosed with anemia, and 6.11% of the study population would be left undiagnosed and untreated for the condition. It is very likely that this undiagnosed percentage translates into a large number of women in the El Alto population who are left untreated for anemia in pregnancy due to insufficient use of altitude-adjusted hemoglobin levels.

Furthermore, this study should be used as an evaluation of various factors of pregnancy outcome in relation to maternal Hb adjusted for elevation. The data demonstrate that maternal anemia was significantly associated with the health of the infant at birth, and that anemic pregnant women gave birth to infants with lower Apgar scores at 1 and 5 minutes following birth than healthy pregnant women. In addition, the prevalence of birth complications in women with maternal anemia was significantly higher than in non-anemic women. The gestation age of the infants was not statistically different between anemic and non-anemic mothers. However, the average gestation age of women with anemia was approximately two weeks less than the average gestation of non-anemic women. The average infant birth weight of women with maternal anemia was 210 grams less than that of women without maternal anemia; however, no statistical significance was determined between the two.

Given the results of the study, it is evident that public awareness of iron-deficiency anemia and its adverse effects must be increased in developing countries. Prenatal care and education from medical professionals is crucial in improving the health of the mother and the developing fetus during pregnancy. Women in all regions of the world need to be taught the importance of this medical care, as well as the value of adherence to vitamin supplementation.

There are still major gaps to bridge in regards to the awareness and treatment of anemia and other health conditions during pregnancy. Using current knowledge, additional studies and effective implementation, public understanding is achievable. Public information sessions and education programs regarding health care during pregnancy and infancy may improve knowledge in El Alto and should be prioritized in the future.

In conclusion, this study sheds light on the fact that the application of altitude-specific hemoglobin adjustments for the diagnosis of anemia is useful in the prediction of pregnancy outcome. Using these adjustment methods, maternal anemia in El Alto, Bolivia, is strongly associated with lower infant Apgar scores at both 1 and 5 minutes following birth, as well as shorter gestational length and higher parity. It is imperative that additional research is done to determine ways to enforce the usage of adjusted Hb cutoffs in pregnancy, most importantly in areas of high elevation. If these cutoffs are correctly used, we can decrease worldwide maternal and infant mortality rates by ensuring that anemic pregnant women receive appropriate medical treatment.

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REVIEW ARTICLE

The Effects of Cognitive Therapy on Hallucinations in Patients with Schizophrenia

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INTRODUCTION

Cognitive therapy was initially developed by Aaron Beck in the 1960s as a short-term psychotherapy for depression (1). It was based on his findings that people suffering from depression exhibit altered cognition along common themes such as low self-esteem, ideas of deprivation, self-criticisms, magnification of problems, self-commands to accomplish tasks which are often large-scale and mutually exclusive, and thoughts of escaping from life's problems. In addition, they tend to employ cognitive distortions such as arbitrary interpretation, selective abstraction, overgeneralization, magnification, minimization, and inexact labelling. These underlying themes and distortions lead to automatic and involuntary depressing and self-deprecating thoughts in various situations, which in turn lead to emotions such as sadness, anger, embarrassment, and anxiety. Beck postulated that depression could be treated through identification and correction of the patient's idiosyncratic cognitions and underlying depressive themes (2). Since then the cognitive model of therapy has expanded to include treatment of many psychopathologies including schizophrenia. This model suggests that cognitive distortions underlie both mood and behaviour in all psychopathologies; cognitive therapy targets and alters these underlying distortions leading to symptomatic improvement (3).

Schizophrenia is a psychotic disorder characterized by two or more of the following for a 1-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and negative symptoms (i.e. affective flattening, alogia, or avolition). Continuous signs of disturbance must be present for at least 6 months, which may include prodromal and residual symptoms in addition to the 1 month of active-phase symptoms (4). While antipsychotic medications are often effective in diminishing symptoms, 10-60% of patients with schizophrenia respond poorly or incompletely to typical antipsychotics and 20-30% of patients taking typical antipsychotics as prescribed will relapse within the first year of maintenance treatment (5). Furthermore, medication non-compliance is a significant barrier to treatment in this population. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that 74% of patients discontinued their antipsychotic medication before 18 months, with discontinuation rates ranging from 64%-82% for various antipsychotics (6). Ayuso-Gutierrez et al. report that 73% of schizophrenia exacerbations requiring hospitalization occurred in patients who were non-compliant with medication (7). As such, adjuvant interventions such as cognitive therapy may be beneficial in treating symptoms that are incompletely responsive to pharmacological treatment or in patients who are non-compliant to pharmacological therapy.

While schizophrenia symptoms include delusions and hallucinations which may be differentially responsive to cognitive therapy, the disease differs from depressive disorders in that patients with schizophrenia have significant impairment in reality testing and often have a considerable lack of insight (8). These characteristics seem to be in direct opposition to those required for cognitive therapy as recognition of faulty cognition is central to its success. A review of various models of schizophrenia is therefore required to understand the aspects of schizophrenia that are amenable to cognitive therapy.

It is widely accepted that schizophrenia is a disorder of dopamine hyperactivity (8), but exactly

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how this hyperactivity creates symptoms of schizophrenia is yet to be elucidated. Kapur's theory of psychosis as a state of aberrant salience builds on research that the mesolimbic dopamine system assigns salience to experienced events and thoughts and transforms them from neutral occurrences to significant entities. Kapur hypothesises that the increase in dopamine in the mesolimbic system of patients with schizophrenia creates inappropriate salience for both internal and external events. Delusions and disorganized thinking in turn result in an attempt to organize disconnected but seemingly salient events into coherent stories (9).

In their literature review, Bentall, Kinderman, and Kaney examine the cognitive distortions in patients with persecutory delusions such as increased attention to threat, a tendency towards external attributions for negative life events, and increased self-esteem when compared to both depressed subjects and controls. They hypothesize that persecutory delusions may be a form of protection from negative information about the self by attributing such information to an external source, thus preserving a positive self-image (10).

Cognitive theories of hallucinations have tended to focus on auditory hallucinations, suggesting that they are related to a defect in speech processing. Inconsistent evidence exists for the claim that sub-vocal activity accompanies auditory hallucinations. Gould showed that patients experiencing auditory hallucinations have greater muscular potentials in vocal muscles compared to controls, as measured by electroencephalograph (11). Green and Kinsbourne were unable to replicate these findings. In addition, they had inconclusive results regarding the effects of decreasing sub-vocalizations on auditory hallucinations: humming decreased the number of self-reported auditory hallucinations by 59% while biting the tongue and holding the mouth open was not associated with a significant reduction (12). The relation of auditory hallucinations to subvocalization has led to the interpretation that such hallucinations are self-generated vocalizations misinterpreted as coming from an external source (13). Consistent with this explanation, in his literature review Bentall examines various theories of hallucinations and concludes that a common theme is the misattribution of self-generated thoughts to an external source (14).

Paralleling Beck's notion that it is one's perception of a situation that governs emotion rather than the situation itself, Chadwick and Birchwood found that patients' emotional reaction during auditory hallucinations was related to their perception of the quality of the voice (malevolent versus benevolent). Malevolent voices triggered anger, fear, depression, and anxiety and benevolent voices triggered amusement, reassurance, calmness, and happiness. Similarly, patients' perceptions of the auditory hallucinations influenced active engagement with or resistance to the hallucination (15).

It is intuitive that delusions may be treated with cognitive therapy as they are distorted beliefs based on misattributions. Following Beck's model, the abnormal cognitions behind the delusional belief can be targeted during therapy. Hallucinations, however, are sensory perceptions rather than faulty cognitions which intuitively makes them less amenable to eradication through cognitive therapy as they are experienced events. Abolishing hallucinations is therefore not the goal of cognitive therapy. Instead, the objective is diminishing the emotional effects that hallucinations have on the patient. This paper reviews a subset of the existing literature on the efficacy of cognitive therapy in treating hallucinations in schizophrenic patients.

METHODS

Articles were identified in Medline using "cognitive therapy", "schizophrenia", and "hallucinations" as search terms which were mapped to subject heading and exploded. The results for these three searches were combined and then limited to randomized control trials, yielding 13 articles. Four articles were not included as they did not investigate the effects of cognitive interventions on hallucinations in schizophrenia. One additional article was obtained via manual search of references in the above articles.

REVIEW

The studies examined in this review belong to three main categories: randomized controlled trials looking at individual cognitive therapy, group cognitive therapy, and hallucination-integrated-therapy (HIT).

Individual Cognitive Therapy

Positive results were found by England for the effects of individual cognitive therapy on "psychiatric symptoms" in voice hearers (16). Individual cognitive therapy was administered by nursing staff to out-patients with schizophrenia and schizoaffective disorder who suffered from auditory hallucinations, in twelve 90-minutes sessions over 4 months. This intervention was associated with a significant

decrease in psychiatric symptoms as measured by total score on the Brief Psychiatric Rating Scale (BPRS) at both 18 and 54 weeks, compared to patients who received usual care. A significant between-group difference was also found for self-esteem as measured by the Robson Self-Concept, a questionnaire that measures self-appraisals in various domains: patients who received the cognitive intervention showed a larger increase in self-esteem as compared to patients who received usual care. Of note, the BPRS includes hallucination severity in its measures but the authors do not specify if hallucination severity in particular is a variable that significantly decreased during the course of treatment. Therefore, these results show only that the cognitive intervention was associated with a decrease in total psychiatric symptoms in patients who hear voices. It can not be concluded that voice characteristics (i.e. loudness, frequency, volume, content) or patient reaction to voices (i.e. distress, compliance) were affected by the treatment.

Trower et al., on the other hand, found promising results for the effects of cognitive therapy specifically on command hallucination compliance in patients with schizophrenia spectrum disorders (17). Cognitive therapy for command hallucinations (CTCH) plus treatment as usual was compared to treatment as usual (TAU) alone in subjects at high risk for command compliance. CTCH was developed by the authors according to the doctrine of social rank theory, which suggests that the appraisal of social subordination and of the power differential between an individual and his persecutor may originate in the individual's appraisal of the social ranking of both the individual and the persecutor (18). Consistent with this theory, the cognitive intervention focused on altering subject perception of voice power and ability to self-direct behaviour rather than on decreasing the frequency or characteristics of the auditory experience. Effect of treatment was evaluated at 6 and 12 months. While both groups showed decreased compliance to commands at both 6 and 12 months, the decrease in the cognitive therapy group was larger (a decrease in partial to full compliance from 100% to 14% after 6 months versus 94% to 39%). While the TAU group showed no change in perceived voice power, voice omniscience, and perceived control over voices, the CTCH group showed a significant decrease in perceived voice power and omniscience, as well as a significant increase in perceived control over commands. These changes persisted at the 12 month follow-up. Of note, the inter-group discrepancy in compliance behaviours at 6 and 12 months was non-significant when using perceived voice power as a covariate, suggesting that perceived voice power is a key factor in governing patient compliance. Further supporting this notion is the fact that voice content did not change in either group, and while perceived voice frequency diminished in the CTCH group at 6 months this decrease was not maintained at 12 months. Therefore, decreased compliance in the CTCH group can not be attributed to changes in voice frequency or content. The CTCH group also experienced a significant decrease in total positive symptoms, negative symptoms, and general psychopathology compared to the TAU group. These results were maintained at 12 months. While distress decreased significantly in the CTCH group at 6 months, this was not maintained at 12 months. Similarly, hallucinations were reduced non-significantly in the CTCH group at 6 months compared to the TAU group, but this difference was no longer present at 12 months.

Tarrier et al. compared two distinct cognitive interventions in schizophrenia patients with medication-refractory psychotic symptoms: coping strategy enhancement (CSE) and problem solving (PS) were compared after 5 weeks of treatment and at 6 months follow-up (19). Coping strategy enhancement involved the identification of existing coping strategies and the use of these pre-existing strategies to outline numerous coping techniques with the aim of coping and controlling both cues and reactions to psychotic symptoms. The authors hypothesized that CSE would improve psychotic symptoms thus decreasing general psychopathology and improve functioning while PS would improve functioning with no specific effects on psychotic symptoms. While all patients receiving treatment showed a significant decrease in number of symptoms and total symptom severity, there was a significant interaction effect of group and time on total symptom severity and a near-significant interaction effect on number of symptoms: the patients receiving CSE showed more change during the treatment period than did the patients receiving PS. Of note, the CSE group exhibited a significant decrease in delusions and a trend towards a decrease in anxiety as measured by the Psychiatric Assessment Scale (PAS) when compared to the PS group. There were no significant changes, however, for the hallucinations subscale. Social functioning was not affected in either group. See Table 1 for a summary of the effects of individual cognitive therapy on patients with hallucinations.

Author	Study Population (n=)	Diagnosis	Experimental Intervention	Significant Outcomes
England (2007)	65	- Schizophrenia - Schizoaffective disorder	Cognitive nursing intervention	- ↓ psychotic symptoms (p<0.0001) - ↑ self-esteem (p<0.001)
Trower et al. (2004)	38	- Schizophrenia spectrum	Cognitive therapy for command hallucinations (CTCH)	**At 12 months:** - ↓ command compliance (p<0.001) - ↓ perceived voice power (p<0.001) - ↓ voice omniscience (p=0.02) - ↓ perceived control over voices (p=0.01) - ↓ positive symptoms (p=0.001) - ↓ negative symptoms (p=0.002) - ↓ general psychopathology (p=0.001) **At 6 months only:** - ↓ distress (p=0.03) - ↓ voice frequency (p=0.022)
Tarrier et al. (1993)	27	- Schizophrenia	Coping strategy enhancement (CSE) vs. problem solving (PS)	- ↓ in number of symptoms for both groups (p=0.0048) - ↓ in symptom severity for both groups (p=0.0013), significantly greater with CSE (p=0.02) - ↓ in delusions with CSE (p=0.019).

Table 1: Effects of Individual Cognitive Therapy on Patients with Hallucinations

Group Cognitive Therapy

Cognitive therapy is a highly specialized form of therapy but is often inaccessible to patients due to factors such as cost or significant wait lists. If group therapy is proven to be beneficial in treating hallucinations in patients with schizophrenia, cognitive intervention can be applied to a larger population.

McLeod et al. found that patients with schizophrenia receiving group cognitive behavioural therapy over 8 weeks showed a significant reduction in voice frequency and in perceived voice power, as well as a trend towards distress reduction at 12 weeks when compared to patients receiving treatment as usual (20;21). It is unclear, however, if these benefits were due to the cognitive behavioural intervention itself, which was aimed at providing patients with a range of coping strategies, or simply to receiving treatment in a group setting.

A study by Penn et al. investigated the effects of cognitive behavioural therapy versus group supportive therapy (ST) on hallucinations in patients with schizophrenia and schizoaffective disorder post-treatment and at 3 and 12 months follow-up, thus controlling for the fact that benefits can be attributed solely to a group setting (22) .

Contrary to the authors' hypothesis, the ST group perceived their auditory hallucinations as significantly less malevolent and showed a trend towards decreased resistance of voices compared to patients in the CBT group, both at 3 and 12 months follow-up. Patients in the CBT group, however, had significantly lower total and general symptoms and a near significant decrease in positive symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) and non-significantly higher levels of insight, but showed no change in voice distress or intensity. These results remained stable from 3 to 12 months follow up.

Of note, the CBT intervention did not attempt to target and modify cognitions surrounding voices, but rather was aimed at increasing coping capability. This may account for the lack of change in patients' perception of voices and concomitant general improvement, an explanation noted by the authors.

Similarly, Wykes et al. found that 7 sessions of group CBT led to a significant improvement in social behaviour at 36 weeks as compared to treatment as usual in a sample of patients with schizophrenia, but neither treatment had any effects on self reported measures of distress and voice topography assessments, such as frequency and loudness, as measured by the psychotic symptom rating scale (PSYRATS). Of note, a cluster effect of therapy on the PSYRATS score was noted, indicating that changes in PSYRATS scores varied between therapy groups. A non-significant association was found between decreased PSYRATS score and both therapist expertise and receiving treatment early in the trial (23).

Hallucination Integrated Therapy

Hallucination-integrated-treatment (HIT) includes several therapeutic modalities: cognitive behavioural therapy, coping training, family treatment, rehabilitative intervention, mobile crisis intervention, antipsychotic medication, and attitudinal and motivational techniques. Of note, HIT differs from other cognitive behavioural interventions in that patients and relatives alike receive the intervention (24).

HIT has been shown to have a significant effect in improving various domains in patients with schizophrenia spectrum disorder suffering from auditory hallucinations when compared to treatment as usual after 9 and 18 months (24;25). In one study, treatment as usual consisted of medication, monitoring and advice, patient and relative psychoeducation, and supportive counselling, while the HIT group underwent a median of 9 months and 11 contacts of HIT. Patient who received HIT showed a significant improvement in quality of life as measured by the World Health Organization Quality of Life Schedule (WHOQoL) at 9 months, which was no longer significant at 18 months. Conversely, both satisfaction with health and global change in Quality of Life score showed a trend towards improvement that became significant at 18 months follow-up. At both 9 and 18 months assessment, patients receiving HIT showed significant improvement in societal involvement, the household, relationship with family, relationship with partner, and as a parent, as measured by the Groningen Social Disabilities Scale (GSDS) (24). In a similar study, patients in both HIT and routine care groups showed decreases in measures of subjective burden at 18 months, significantly greater in the HIT group for negative content, distress, and total burden. HIT treated patients also showed significant improvement in positive symptoms and disorganization, and a trend towards significant improvement in depression, general psychopathology, and total PANSS score (25). These results show promising results with regard to overall functioning and quality of life, but again do not necessarily indicate hallucination-specific effects of cognitive intervention.

Jenner et al investigated routine care versus HIT and found hallucination-specific results (26). HIT was given in approximately 20 one-hour

Author	Study Population (n=)	Diagnosis	Experimental Intervention	Significant Outcomes
McLeod et al. (2007)	10	Schizophrenia	Group cognitive behavioral therapy	- ↓ voice frequency ($p<0.01$) - ↓ perceived voice power ($p<0.01$)
Penn et al. (2009)	65	Schizophrenia spectrum	Group cognitive behavioral therapy (CBT) vs. enhanced group supportive therapy (ST)	- ↓ voice malevolence with ST ($p=0.044$) - ↓ total symptoms with CBT ($p=0.019$) - ↓ general symptoms with CBT ($p=0.02$)
Wykes et al. (2005)	85	Schizophrenia	Group cognitive behavioral therapy	- Improvement in social behaviour ($p=0.018$)

Table 2: Effects of Group Cognitive Therapy on Patients with Hallucinations

Author	Study Population (n=)	Diagnosis	Experimental Intervention	Significant Outcomes
Wiermsa et al. (2004)	63	Schizophrenia spectrum	Hallucination integrated treatment	- ↑ quality of life at 9 months ($p<0.05$) - ↑ satisfaction with health at 18 months ($p<0.05$) - ↑ total score of WHOQoL at 18 months ($p<0.05$) - ↑ numerous domains of social functioning ($p<0.01$-$p<0.05$)
Jenner et al. (2006)	63	Schizophrenia spectrum	Hallucination integrated treatment	- ↓ total subjective burden ($p=0.02$) - ↓ negative content ($p=0.02$) - ↓ distress ($p=0.01$) - ↓ positive symptoms ($p=0.05$) - ↓ disorganization ($p=0.01$)
Jenner et al. (2004)	76	Schizophrenia spectrum	Hallucination integrated treatment	- ↓ distress ($p<0.05$) - ↓ total burden ($p<0.05$) - ↓ positive symptoms ($p<0.001$) - ↓ disorganization ($p<0.05$) - ↓ general psychopathology ($p<0.01$) - ↓ total PANSS score ($p<0.01$)

Table 3: Effects of Hallucination Integrated Treatment on Patients with Hallucinations

sessions over 9-12 months in patients with schizophrenia spectrum disorders suffering from auditory hallucinations. Routine care was given in an equal number of contacts and total contact time and post-treatment effects were measured at 9 months. While patients in both groups showed decreased severity in the Auditory Hallucination Rating Scale (AHRS), the HIT group showed a significant decrease in distress and total burden on the AHRS as compared to the routine care group. Furthermore, the HIT group showed a significant improvement in PANSS positive symptoms, disorganization, general psychopathology, and total score as compared to the routine care patients. Depression levels showed more improvement in the HIT group as well but did not reach significance. While HIT focused on decreasing the number of applied coping strategies to promote consistent strategy use, patients in the HIT group showed a non-significant decrease in number of coping strategies compared to those with routine care and showed a greater use of empowerment and normalization post-treatment (70% and 57% respectively).

DISCUSSION

Taken together, these studies yield equivocal results regarding hallucination specific outcomes from both individual and group cognitive interventions, as well as from HIT. This lack of consistent results may be due to insufficient study power to detect small to moderate differences between groups. At the same time, these results may also be attributed to the fact that cognitive behavioural therapy and HIT have many components. Some of these components may not focus on hallucinations per se, which can account for the lack of hallucination-specific effects and simultaneous positive outcomes in other areas. Future research that focuses on treating characteristics of and patient reaction to hallucinations, similar to the research conducted by Trower et al (17), may yield more promising results. For example, in patients who hear self-deprecating voices, subjective levels of distress can be evaluated following an intervention that targets patients' perception of content validity. Similarly, in patients who hear voices that encourage or discourage behaviours based on contingent outcomes (i.e. if you do X, Y will happen), patient behaviour can be eval-

uated following an intervention that targets patients' perception of voice omniscience.

On the other hand, the effects of decreasing total, positive, and general symptoms and improving socialization and subjective quality of life should not be dismissed. Patients with schizophrenia tend to be isolated. In a sample of 74 out-patients with schizophrenia, 16.2% lived with a spouse or child, 8.1% lived with an extra-marital partner, 37.8% lived alone, and 31.1% lived with parents. The remainder lived in rehabilitation centres or hostels. A majority (63.5%) of the sample was single, with only 57% of patients interacting with non-relatives (27). Therefore, interventions that are successful in improving social behaviour may prove to be beneficial in this isolated population as they may lead to increased socialization and decreased isolation. Furthermore, Curson et al. showed a high negative correlation between improvement in socialization as measured by the Social State Rating (SSR) and number of schizophrenia relapses in a 7 year follow-up study (28), and Rajkumar and Thara showed a significant difference in number of social contacts of patients with schizophrenia who suffered a relapse as compared to those who did not (2.31 and 4.27 respectively) in a 3 year prospective study (29). In addition, life satisfaction as measured by modified quality of life scales has been shown to be associated with suicide, with lower satisfaction levels increasing the suicide-risk in a 20-year follow up study of adults who were not selected based on mental health (30). It follows then that increasing socialization may decrease the risk of schizophrenia relapse while improving subjective quality of life may decrease suicide risk.

This review has several limitations. Firstly, it is not exhaustive of the randomized controlled trials on this subject. In addition, the articles reviewed did not all investigate the same treatments or populations despite being results of the same literature search; some articles included only patients with schizophrenia while others included the entire schizophrenia spectrum. Some articles examined cognitive therapy while others investigated hallucination-integrated treatment. It is also not possible to determine what components of a mixed-modality treatment such as HIT are responsible for any change in the experimental group. In the same vein, the application and content of cognitive therapy may differ between and within studies, as well as between patients and therapists. As a result, it becomes difficult to determine which aspects of a uni-modality treatment are therapeutic as treatment is both therapist and patient dependant.

The American Psychiatric Association defines recovery as "…a person's capacity to have hope and lead a meaningful life…The concept of recovery values include maximization of 1) each patient's autonomy based on that patient's desires and capabilities, 2) patient's dignity and self respect, 3) patient's acceptance and integration into full community life, and 4) resumption of normal development. The concept of recovery focuses on increasing the patient's ability to successfully cope with life's challenges, and to successfully manage their symptoms" (31). While the studies examined in this review do not show consistent hallucination-specific effects or complete eradication of symptoms as a result of cognitive interventions, they show that such interventions promote recovery as defined by the APA. Perhaps, then, the challenge that remains is not to find interventions that are hallucination-specific or that aim to eliminate symptoms, but rather to promote acceptance of this new definition of recovery.

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REVIEW ARTICLE

Engineering Alloplastic Temporomandibular Joint Replacements

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ABSTRACT: Temporomandibular disorders (TMD) are part of a heterogeneous group of pathologies that manifest with a constellation of signs and symptoms. They are the most frequent cause of chronic orofacial pain and are prevalent in 12% of the general population. Despite the debilitating nature of these disorders, there is no standardization for treatment of the diseased temporomandibular joint (TMJ). In this review, we present an overview of the functional anatomy of the TMJ and the engineering concepts that must be understood to better understand the indications for surgical management, the types of available treatments and the requirements for reconstruction. A comparison is made of the clinical outcomes with autogenous versus alloplastic reconstruction, including a history of alloplastic materials and the design features of currently available implants. Emphasis is made on material selection, modulus, stiffness, notch sensitivity and modularity. For the treatment of TMD, engineered TMJ alloplastic replacements have had considerable promise with additional room for improvement using new materials and recent design concepts.

KEYWORDS: Temporomandibular joint (TMJ), alloplastic, prosthetic, artificial, replacement, arthroplasty, reconstruction, engineering

INTRODUCTION

The temporomandibular joint (TMJ) is one of the most active joints in the human body. This unique “ball and socket” joint allows for more than 2000 hinge and sliding motions per day in activities such as talking, swallowing, and kissing. Temporomandibular disorders (TMD) are currently the most prevalent source of orofacial pain accounting for 12 percent of the adult population in the United States (1, 2). There is a strong 10:1 female predominance with the majority being between eighteen and forty-five years of age (1-3). Congenital dysmorphism, trauma, osteoarthritis, rheumatoid arthropathy, ankylosis, condylar resorption, neoplasia, and previous failed reconstruction of the TMJ attribute to the development of TMD and are indications for TMJ reconstruction (4, 5). The presenting symptoms include headaches, changes in the mandibular range of motion, and pain (1, 6, 7). Despite the significant psychosocial impact of TMD, the method of TMJ reconstruction remains controversial. Currently, autogenous and alloplastic joint replacements are available. The purpose of this review is to discuss the advantages and disadvantages of current TMJ replacements with an emphasis on engineering concepts and future improvements.

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TEMPOROMANDIBULAR DISORDERS

Pathogenesis of degenerative TMJ diseases is thought to occur from the disequilibrium processes involving chondrocyte proliferation, differentiation, and degradation. Coupled with increasing

inflammatory mediators, the hallmark of TMD is increased degradation of the joint tissue. Altered mechanical loading, female hormones, and alterations in the extracellular matrix of the TMJ are thought to cause TMD (8). Altered mechanical loading by either trauma or distorted function can surpass the healing capacity of the joint and cause irreversible damage (9, 10).

Traumatic injuries can also result in degenerative changes of the TMJ. Comminuted fractures of the mandibular condyle are difficult to treat and can lead to chronic pain and ankylosis. A study of 400 TMD patients found that a quarter of the cases were linked to a traumatic event (11). Whiplash injuries seemed to be especially linked to the development of painful jaw and the development of delayed TMD symptoms (12, 13).

In addition to mechanical etiology, genetic predisposition has also been linked to TMJ symptoms. The high prevalence of TMD in women has been correlated with estrogen and progesterone levels. In addition, the intensity of jaw pain has been associated with polymorphisms in the estrogen receptor (16). In addition to hormonal influences, genetic predisposition to TMD is also postulated to affect the joint extracellular matrix (14, 15).

Irrespective of the etiology of TMD, the symptoms can be devastating to the patients suffering from the disease. Consequently, the goals of TMJ reconstruction should be to: 1. reduce patient suffering; 2. improve joint function; 3. reduce disability; 4. prevent morbidity; and 5. maintain acceptable treatment costs (17). To better understand how to achieve these goals, an understanding of the TMJ anatomy and function is required.

ENGINEERING CONCEPTS OF THE TEMPOROMANDIBULAR JOINT

The TMJ can be simplified as a “ball and socket” joint. The mandibular condyle “ball” fits into the temporal bone mandibular fossa “socket” (Figure 1). It is capable of both rotational and translational motion. The ability of sliding on a hinge joint is unique to the TMJ. This allows for motion in various vector planes involved in speech, mastication, swallowing, and yawning (3).

This ball and socket lever system has an articular disc separating the mandible and the temporal bones. This avascular, insensate structure is attached to the condyle medially and laterally by collateral ligaments (Figure 1). Cartilage is found on the bony surfaces in the TMJ allowing for the dissipations of shearing and frictional loads generated by the functional jaw. Synovial fluid that bathes the TMJ acts as a vehicle for nutrient delivery and waste product removal. It also acts as a lubricant by reducing the coefficient of friction and the strain energy (18).

Functionally, the forces of mastication are distributed along the mandible. The tensile stresses develop at the sites of masseter muscle attachment to the bone which are converted to compressive stresses at the bite target. The forces are distributed (flow) through the stiffest components of the bone to the target point. This is the cortical part of the mandible ramus and body. At the target, the teeth and adjacent bone experience the maximal compressive stress. This stress continues to increase at the bite target until the geometry of the target changes (cleaving or crushing). The contralateral masseteric sling generates force that acts to stabilize the mandible from rotation. In addition to this TMJ hinge motion, the chewing and grinding of the found bolus require translational and sliding forces in the axial plane generated by the pterygoid muscles. Aberrant mechanical loading because of trauma or even changes from solid to soft diet

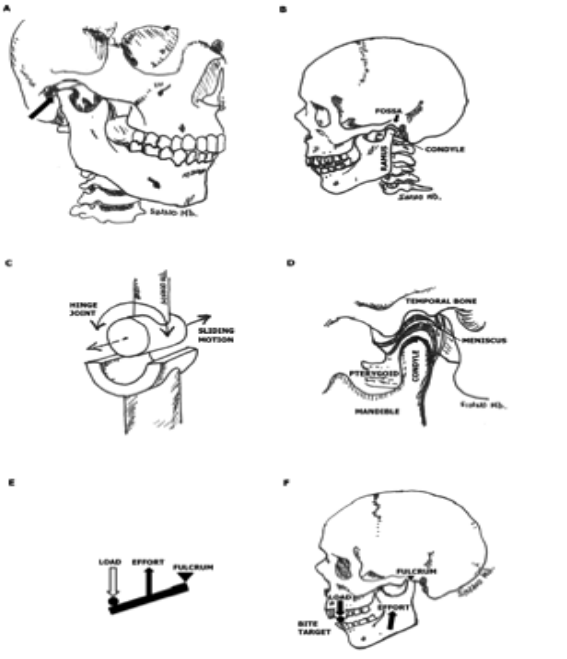

Figure 1.:A) Black arrow pointing to the anterolateral view of the TMJ as seen on a drawing of the human skull. B) Drawing of the left lateral TMJ on a human skull. C) A schematic of the TMJ as a hinge and sliding joint. D) Saggital section through the TMJ showing the meniscus and cartilage between the mandible and temporal bones of the TMJ. E) The jaw simplified as a third class lever: Lever: the mandible body; Fulcrum: the TMJ; Effort: force generated by the masseter muscle; and Load: the food bolus. F) Drawing of a lateral view of the human skull as a third class lever with a bite target as the load.

can cause decreases in the thickness of the mandibular condylar cartilage and subchondral bone volume which can be reversed with the restoration of normal loading (9,10,19). In addition, the forces generated with mastication can generate high joint reactive forces on the condylar cartilage. Accumulation of abnormal forces, trauma, and autoimmune reactions can wear the normal TMJ and lead to TMD. This can be a devastating, painful state that prevents normal jaw function and may also lead to bony resorption. TMJ reconstruction surgery can be an option to reverse these changes.

RECONSTRUCTION OF THE TMJ

AUTOGENOUS

The initial management of TMD includes occlusal splints, physiotherapy, pharmacotherapy and complementary medicine. Surgery is offered as a last resort since it has been shown that the higher the number of prior jaw surgeries, the poorer the subjective outcome (20). Most authors agree however, that the main indications for joint replacement are the presence of a symptomatic severely damaged joint from either severe joint disease or failed previous surgeries.

The method of reconstruction of the TMJ with autogenous grafting versus alloplastic prosthetics is controversial. Many autogenous grafts and flaps have been described including fibula, metatarsal, sternoclavicular, iliac, and costochondral tissue (21). The most commonly used technique is the costochondral graft (Figure 2). This graft is unique in its biological compatibility, workability, functional adaptability, and minimal detriment to the patient. The growth potential of costochondral grafts is ideal in children. Cost has also been implicated as an advantage over alloplastic prosthetics. To our knowledge however, there are no cost analysis studies comparing the longer operative time and hospitalization required for patients undergoing autogenous TMJ reconstruction as compared with the initial high cost of alloplastic implants. Autogenous grafting for TMJ reconstruction has shown very satisfactory cosmetic and functional results. Complications do exist however, including donor site morbidity, facial and temporoparietal nerve injury, Frey's syndrome, recurrence of ankylosis, fracture, bone resorption, and unpredictable growth behaviour of the graft (22, 23). Another important consideration is that autogenous reconstruction only deals with the mandibular condyle portion "ball" of the joint. It does not address abnormalities of the temporal bone mandibular fossa "socket". Furthermore, when autogenous reconstruction was compared with alloplastic reconstruction of the TMJ, patients showed equal improvement in pain and jaw function (21). However, more patients required re-operation in the autogenous group (66.67%: n=18 of 27), a third of who developed recurrent ankylosis (21). Autogenous grafting for TMJ reconstruction can be a satisfactory operation in the right patient with a known complication.

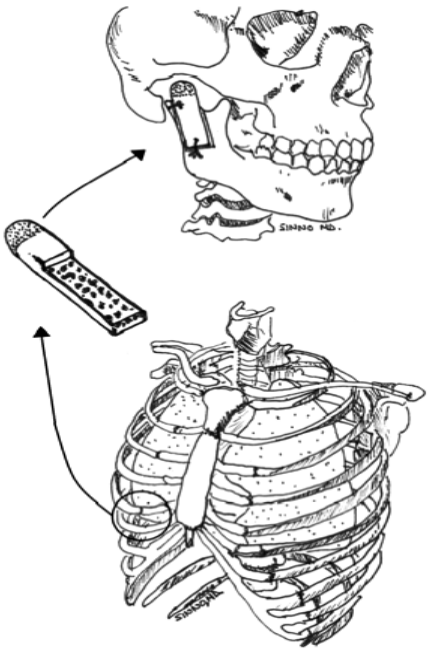

Figure 2: Drawing of the harvest of the costochondral rib graft for temporomandibular joint reconstruction. The decorticated rib graft is fit into the mandible as an inlay and fixed with 0.5 mm stainless steel wires.

ALLOPLASTIC

Indications for alloplastic TMJ reconstruction are controversial. Mercuri has summarised the indications in his review: 1. Ankyolosis with severe anatomic abnormalities; 2. Failure of autogenous grafts; 3. Failure of Proplast-Teflon or Vitek-Kent or partial joints implants; 4. Severe inflammatory joint disease that results in joint mutilation and functional disability (17). Unfortunately, due to the lack of current data, these criteria have been presented without the discussion of differences between available prosthetic options.

History

In light of the disadvantages in autogenous reconstruction, alloplastic TMJ reconstruction was increasing in popularity in the early 1980's. At that time, Vitek Inc. obtained FDA-approval for the use

of their Proplast-Teflon implant designed for surgical replacement of dysfunctional TMJ. Proplast was developed by a chemical engineer, Dr. Charles Homsy, in the late 1960's. He combined this soft porous material with Teflon (polytetrafluoroethylene) resin to create a biomedical implant for TMJ replacement. The Proplast was used to encourage host tissue ingrowth and stability while the Teflon was designed to withstand wear from the joint. Homsy studied his materials in vitro, however he did not conduct wear nor animal testing of the Proplast disc implants (24). Despite incomplete testing (25) and warnings given by the supplier company Du Pont that "Teflon implants wore badly and had a tendency to disintegrate in load bearing joints" (26), it is estimated that 26,000 patients across North America were fitted with these implants. By the late 1980's many patients presented with irreversible and life altering symptoms related to mechanical failure of the Vitek product. This was secondary to the implant failure under repeated loading causing soft tissue damage. On January 1991, the FDA ordered Vitek to remove its implants from the market.

Implant Design

Engineering Concepts:

To prevent repeating the Vitek implant catastrophe, thorough testing of materials for implant design must be conducted. In the world of total hip arthroplasty (THA), various materials have withstood the test of time for the past four decades. It would seem reasonable therefore to look at orthopaedic technology for better solutions to problems in craniofacial surgery. Choosing the appropriate materials, however, begins with understanding key engineering concepts and desirable implant properties.

Biocompatibility: The first tenet of implant design is to attain good fixation while causing the least amount of damage to the surrounding tissue.

Modulus: The elastic modulus of a material is the measure of resistance to deformation for a given load or stress. For example, materials with lower elastic moduli or lower function stiffness (see below), are generally more load sharing with bone, a property that helps preserve native bone density and strength.

Stiffness: The stiffness of a material is dependent on both the elastic modulus and geometry of the device (equivalent to the arithmetic product of the two values). For two objects made of the same material, the larger the object the stiffer it is and thus, more resistant to deformation. One way to use relatively rigid metallic materials without necessarily creating an implant that is excessively stiff is to make the implant hollow or very porous. This design concept enables the fabrication of implants that better share load with bone (see below).

Stress Shielding: When different materials are placed adjacent to one another with a uniform load applied to both, the stiffer material will resist changes in deformation more than the more flexible material. For example, when a titanium metal plate (a higher modulus of elasticity than bone) is fixed adjacent to bone, stresses applied will be seen by the stiffer metal plate (Figure 3). Bone is said to be "stress shielded". According to Wolff's Law, bone will remodel according to in vivo loads; thus bone that is 'stress shielded' will lose density and consequently have less mass and strength in the case of revision surgery.

Notch Sensitivity: In addition to reducing stress shielding, promotion of bone ingrowth through porous metal coating will also increase implant fixation. The porous coating of hip implants has been shown to promote bone ingrowth (30-32). The ingrown bone rigidly fixes the implant and prevents pain and implant-host interface failure. The addition of a porous coating to the surface of implants however, causes stress concentrators that may propagate a fracture in notch sensitive material. Notch sensitivity is the degree to which the sensitivity of a material to fracture is enhanced by the presence of a surface inhomogeneity such as a notch created by surface porous coating. Notch sensitive materials are also prone to fracture at sudden changes in section, cracks, or scratches. In

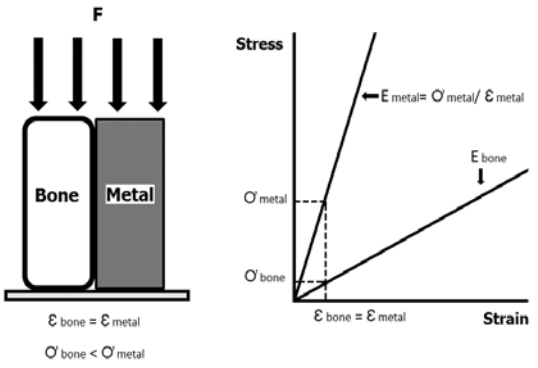

Figure 3: The load deformation curve on the right demonstrates that metal has a higher modulus than bone. More stress is required to deform metal than bone for a given strain. On the left, is a schematic of metal stress shielding bone for a given force F: Force; O': Stress; ε: Strain=(L2-L1)/L1, where L1 is the initial length, L2 is the length after deformation; E: Modulus of Elasticity

general, ductile materials are less notch sensitive than brittle materials.

Modularity: Modularity is another important concept in implant design, enabling the advantageous use of different materials for specific functions. For example, materials optimized for wear resistance can be used for the bearing components while materials that are less stiff can be used for load carrying and fixation to reduce stress shielding and consequent bone resorption.

Materials:

The same materials that are utilized in hip and knee arthroplasty are applicable to TMJ replacement. Cobalt-chromium and titanium alloys possess the necessary strength and fatigue resistance for implant stems and bodies, with titanium alloy having the advantage of lower elastic modulus and better load sharing characteristics. A variety of porous fixation surfaces are available for enhancing stability through tissue ingrowth. They include the more traditional beaded or fiber wire types of surface treatments and the newer higher porosity foam-like materials made of either titanium or tantalum (33-37). Potential bearing combinations include cobalt-chromium alloy against polyethylene or a hard-hard bearing using alumina oxide ceramic or cobalt-chromium alloy. Of significant note is the fairly recent development of highly cross-linked polyethylene, a very wear resistant formulation of ultra high molecular weight polyethylene that is witnessing widespread use in total hip and knee arthroplasty. Wear simulator studies have confirmed very low wear rates with these new materials (37-40).

With the knowledge of implant design specifications, the appropriate component materials can be chosen. Among those, there is stainless steel. Such a material has appropriate ultimate tensile strength and fatigue properties. It should be avoided for TMJ implants however, as it is susceptible to crevice and inter-granular corrosion: in active areas such as the TMJ, this corrosion may lead to implant failure and consequent immune reaction and osteolysis. Stainless steel is not “biocompatible” under the loading conditions found in the TMJ. Cobalt-Chromium (CoCr) based alloys are biocompatible and unlike stainless steel are highly corrosion resistant. They have low notch sensitivity and thus can be treated with metal beads or fibre wire to promote bone ingrowth and significantly increase implant fixation (33). CoCr alloy metals have excellent wear properties and have stood the test of time in metal on metal hip implants for up to 20 years (34). CoCr is very hard and abrasion resistant, but this property can be a disadvantage in TMJ implants. Due to its high elastic modulus, CoCr alloy implants cause significant stress shielding (35). Examples of implant migration and bone fracture secondary to the profound bone resorption have been reported in the orthopedic literature (35).

Titanium alloys are highly biocompatible with half the elastic modulus of CoCr. As a more flexible implant, it can more uniformly transfer loads and cause significantly less stress shielding to adjacent bone. Titanium however does not have good wear properties. When subjected to repetitive forces, it is fatigue resistant and thus breaks down. It should not be used at the joint interface. Furthermore, titanium is notch sensitive and thus should not be impregnated with beads or fibre wire to promote bony ingrowth. However, when the surface is roughened without notching, bone ongrowth occurs and thus improves fixation. Consequently, non-porous coated titanium alloy material can be used for the TMJ stem component to decrease stress shielding to the adjacent bone while still withstanding the forces generated at the TMJ. CoCr on the other hand has excellent wear resistance and is the reason why it is used as the femoral head component in total hip arthroplasty. It can withstand the high repetitive motion and forces up to three times body weight with acceptable wear properties lasting an estimated 20-30 years. Consequently CoCr is an ideal material for the “ball” component of TMJ alloplastic implants.

Non-metallic materials have a significant role in joint replacement as well. Ceramics for example, are very stable and inert materials that can withstand high compressive forces. They are brittle however, and are susceptible to fracture when subjected to high tensile forces. They have been shown as useful alternatives as bearing material in highly loaded joints such as the hip.

Ultra-high molecular weight polyethylene (UHMWPE) has also had long term success in the orthopaedic literature as a joint spacer in the hip and knee (36). With repetitive loading however, it is subject to wear. To prevent particularization, osteolysis, and aseptic loosening, cross-linked ultra-high molecular weight polyethylene with improved wear resistance has been developed (37-39). Hip simulator studies have confirmed very low wear rates with these new materials (38, 40).

Contemporary metal-on-metal CoCr bearings have shown very low wear rates as compared to polyethylene. They have however been shown to release particles and ions from the articulating

surfaces into the joint and the whole organism especially in the early phase after implantation. The released metal ions, especially chromium, are hypothesized to potentially trigger cytotoxic, carcinogenic and allergic reactions. The incidence of these implant-related complications is very low but long term data is unavailable. More research is required for the development of the best and safest bearing choice for implant design.

CURRENT IMPLANTS

Three prosthetic systems currently exist: 1. TMJ Implants (41); 2. TMJ Concepts (42); and 3. Biomet/Lorenz (43). Similar to hip implants, they are a "ball and socket" type of prosthetic joint. The three systems differ in their component materials (Table 1).

The condylar portion of all implants is made of CoCr alloy. The Biomet/Lorenz TMJ implants have a plasma spray titanium coating on the bone-contacting surface that allows bone apposition and biologic fixation. The CoCr bearing has high hardness and strength and attaches to the implant body with a modular taper connection.

Attached to the condylar component is the ramus which is made of CoCr alloy for the TMJ Implants and the Biomet/Lorenz system. The TMJ Concepts utilizes titanium alloy. Unlike the hip, the mandible is a thin bone that does not have much volume for implant fixation. The smaller modulus of titanium would better distribute load and decrease stress shielding in the inherently thin mandibular bone.

Connecting the "ball" to the "socket" is the fossa component. The TMJ Implants utilizes a metal-on-metal bearing made of CoCr alloy. Both the TMJ Concepts and the Biomet/Lorenz systems utilize UHMWPE for the fossa bearing material. Metal-on-metal components have been shown to have high wear resistance and long life expectancy in the hip. However, in the jaw where loads are relatively high and contact areas are smaller and less congruent than in the hip, there is potential for a more aggressive wear environment due to higher contact stresses. This is equally true for the CoCr-UHMWPE bearing components of the TMJ Concepts and Biomet/Lorenz systems. All three systems utilize titanium alloy screw for implant fixation to bone. The current available data for all implants have been promising. In 2004 Mercuri and Giobbie-Hurder showed high success rates with TMJ Concepts systems with a follow-up period of 60 months (44). Saeed and Speculand independently reviewed their use of the TMJ Implants on a total of 154 patients with acceptable outcomes (21, 45). The Biomet/Lorenz system was reviewed in a case series describing the manufacturer's results (46). The objective outcomes of jaw function were shown to be highest in the multiply operated patients (3). These patients had poorer subjective responses however, which was attributed to psychological factors (3). Moreover, total alloplastic TMJ replacements have shown promising treatment outcomes reporting decreased patient pain and improved jaw function.

	Fossa	Condyle	Ramus
TMJ Implants	Co-Cr-Mo Alloy	Co-Cr-Mo Alloy	Co-Cr-Mo Alloy
TMJ Concepts	Ti (UHMWPE surface)	Co-Cr-Mo Alloy	Ti Alloy
Biomet/Lorenz	UHMWPE	Co-Cr-Mo Alloy (Ti surface)	Co-Cr-Mo Alloy

Table 1: Components of the three TMJ prosthetic systems. Co: cobalt; Cr: Chromium; Mo: molybdenum; Ti: titanium; UHMWPE: ultra-high molecular weight polyethylene

Alloplastic TMJ reconstruction devices have shown considerable predictability and reliability. Many advantages exist over autogenous grafts: 1. Immediate jaw motion and physiotherapy; 2. No need for secondary donor site; 3. Custom made alloplastic implant capability. The immediate capability for patients to undergo physiotherapy is perhaps the most important advantage of alloplastic implants. The patient's mandible is able to immediately function after implantation and thus continuous active and passive muscle activity allows for improved outcome and decreased stiffness of the joint. The decrease in secondary donor site morbidity is also a very attractive option over autogenous grafting. Not only does it prevent complications to other sites of the body, but operative time and costs are also decreased. Alloplastic materials can also be custom made to mimic the normal anatomic contours of the structures they are to replace. They can therefore be better stabilized and allow for faster recovery time.

Despite the many advantages to alloplastic prosthetics, there are known limitations. Alloplastic prosthetics are contraindicated in children, non-informed patients, in patients with uncontrolled systemic disease, in patients allegic to these materiels, and finally in patients with an active infection at the site of implantation (17). They should not be used in children as the implants may interfere with the normal growth of the facial skeleton and they would need to be replaced when facial maturity is reached. Another limitation of alloplastic prosthetics is their initial implant cost. The relative novelty of

the modern TMJ implants limits the long-term data regarding material wear, failure, and implant stability.

FUTURE DIRECTION / CONCLUSION

Generalization of the improvements in patients undergoing total alloplastic TMJ replacement is limited to the low number of studies and the few surgeons and manufactures available. New technologies have been described in different fields that can improve current TMJ implants. For example, the use of cross-linked UHMWPE for the TMJ fossa may prove superior in wear to the current available implant materials. In addition, bisphosphanates are a group of anti-osteoclastic agents that have an anti-resorptive effect used in osteopenic patients for reducing bone resorption, increasing bone density, and decreasing fracture incidence. Studies have showed maintenance of bone mineral density around bisphosphanate impregnated hip implants (47, 48). The same technology may be applied to the TMJ implants to counter the stress shielding effects on the mandible. Another promising field advancing TMJ reconstruction technology is tissue engineering. Recent studies have manipulated rat bone marrow mesenchymal stem cells to form the shape and dimensions of a human mandibular condyle (49, 50). Such technology may provide anatomic-specific autogenous tissue implantation with the potential to adapt to the functional loads in the TMJ. Moreover, long-term clinical studies and improved implant design can potentially further improve the current available technology and help the millions of patients suffering from TMD disorders.

To conclude, the goal of TMJ reconstruction should appropriately address the presenting complaints of the patients without causing harm. Both autogenous and alloplastic TMJ reconstruction are available surgical options. Autogenous reconstruction is indicated in children as these grafts have growth potential. Modern alloplastic TMJ reconstruction has also shown improved subjective and objective outcomes with fewer complications than autogenous grafting. Long-term data however are insufficient to appropriately predict the life expectancy of the alloplastic systems. With understanding of the functional anatomy of the jaw and the engineering concepts and mechanics of the TMJ, superior designs and long-term studies can improve the systems currently available.

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CROSSROADS

Male physicians treating Female patients: Issues, Controversies and Gynecology

Jacques Balayla*

INTRODUCTION

The most precious and sacred form of personal information that we possess is our body. It is our own flesh and blood, which holds and sustains our being. Our body is our instrument for living. It is so personal and intimate that we frequently hide it, as though its public display would be a natural source of shame. Michel de Montaigne, the French Renaissance author, puts it well: "Man is the sole animal whose nudity offends his own companions and the only one who, in his natural actions, withdraws and hides himself from his own kind" (1).

Thus, it not surprising that visiting a physician and allowing for an intricate inspection and examination of our dearest possession, our body, is a source of trepidation and anxiety for us. Perhaps the deepest level of vulnerability in an exam is the genital and pelvic examination. A glimpse into history demonstrates that until very recently, pelvic examinations in women were handled by females, likely to ensure comfort and privacy all the while preventing improper interactions from male counterparts.

HISTORICAL PROGRESSION OF THE PELVIC EXAMINATION

The oldest medical text known to man is the "Kahun Gynecological Papyrus", written by the Egyptians around 1800 BCE. The papyrus provides a glance into early gynecological medicine and unveils the traditions of reproduction, conception and delivery in ancient Egypt. For the Egyptians, the main treatment modalities provided by the ''swnw'' (pronounced sounou, physician figure) were founded on pharmacopoeia from animals, plants and minerals; surgical intervention was never recommended (2). Magic spells were whispered, as it was believed that diseases were demonic in origin.

Due to compliance with religious doctrine, men were not allowed to be present at births or at other rituals that dealt with the intimate parts of a woman. Instead, it was the role of the midwife to take care of women and to assist them with their gynecological needs. Interestingly enough, the "Kahun Papyrus" provides some of the earliest evidence of midwifery in history.

Similarly, in the middle ages, it was often the norm for a woman's sexual organs to be examined by midwives, nurses or other females who previously had had similar problems to the patient's. By the early 1800's, with the advent of modern medical degrees and physical examinations, the pelvic exam began to be performed by male physicians, as women were not allowed to enroll in medical school. However, this examination was a variation of the modern version as it consisted of a "compromise" in which the physician kneeled before the woman but did not directly inspect her genitals, only palpated them. In addition, it was during this period that the use of a chaperone became a part of the clinical examination. The chaperone's role was to emotionally support and reassure the patient during a procedure that she found embarrassing or uncomfortable. The chaperone also acted as a witness in cases of malfeasance by the physician. Today, in many parts of the world where religious and cultural precepts often discourage female encounters with male physicians, chaperones still attend gynecological examinations.

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By the 1970's, only 9% of enrolled medical students in the United States were women (3). The numbers have drastically increased since then: now 58% of medical students are women (4), yet there are still disparities in gender among the specialties. In Obstetrics and Gynecology, female residency enrolment rates have quadrupled from 1978 to the present, leaving men in the minority (women account for 71.8% of Obs/Gyn residents today). Between 1989 and 2002, the proportion of female Ob/Gyn residents rose from 44% to 74% while the proportion of female graduating medical students only increased from 33% to 44% (5).

As though influenced by the media, the observed trend among medical school graduates today is one where males are over-represented in surgical specialties and females are over-represented in Obstetrics & Gynecology and Pediatrics, practices typically associated with the maternal role. Hence, it is well observed that throughout history and up until recent years, the male role in gynecology has been absent, indirect, or directly overlooked by a third party.

A DISPROPORTIONATE REPRESENTATION: REQUIRED OR STEREOTYPICAL?

The question of why female physicians are more attracted than men to Obstetrics & Gynecology programs is an interesting one. Is there truly a belief that women in the population are more comfortable being treated by women, especially in the context of sexuality? Or is this over-representation rooted in the desire of female doctors to project their own image and health onto the women that they treat? Conceivably, as Dr. Nelson Soucasaux puts it, it may be due to the fact "...that a great number of men have considerable psychological problems in relation to women and that the male psyche is naturally directed towards the female sex" (6) which makes some men uncomfortable and less willing to make a living treating women. While the true source of this disproportionate representation remains unclear; the literature provides interesting insight into societal views on the subject: A study from the department of Obstetrics and Gynecology from the University of Connecticut found that 66.6% of patients had no gender bias when selecting an obstetrician-gynecologist. In addition, 80.8% of patients felt that gender did not influence quality of care (3). These numbers suggest that there are factors other than gender that come into play when choosing a gynecologist. As demonstrated in the primary care literature, interpersonal style and communication appear to be the most important traits in physicians rather than gender (7).

THE MALE MEDICAL STUDENT PROBLEM

Clinicians have, consciously or unconsciously, come to realize that less negotiation for consent to involve a student in a pelvic examination will be needed if the student is female (8). A study from the Kingston General Hospital showed that 72.8% of clinic patients reported they would accept an intimate examination by a medical student of either gender, compared with only 32.1% of high school students. In addition, 22.2% of clinic patients indicated they would only accept a female student, in comparison to 55.3% of high school students who would do the same. This seemingly contradictory result demonstrates that as women move forward through the life cycle, gender bias is less observed. In reality, the proportion of subjects preferring female medical students was inversely related not to age, but rather to the number of previous breast or pelvic examinations (9).

Regardless of gender preference, various statements supporting medical student participation in intimate physical examinations were rated as "important" or "very important" by the majority of clinic patients and secondary school students alike.

Over the last two decades there has been an increase in demand for gynecologists and other women's health specialists. Though enrolment rates continue to rise in North American residency programs, waiting lists for screening tests and other basic gynecologic procedures are still markedly long. One of the many ways to respond to this demand is to foster the male interest in the specialty in medical students, in the hopes to augment the male enrolment rate later on. Why males specifically? Evidence shows that any stigma associated with being a "male gynecologist" is no longer accounted for, as the vast majority of patients don't necessarily prefer a female gynecologist over a male one. This misperception has been reinforced over the years by anti-male obstetrician-gynecologist biases in articles and advertisements published in popular women's magazines. Unfortunately, men in particular appear to be influenced by what they perceive as patient desire and the trends of the profession (9).

Positive early experiences with pelvic exams and general gynecology are a key determining factor in pushing a male medical graduate to consider a career in gynecology. Studies have shown that teaching programs involving

professional patients are superior to teaching and learning on plastic models for both psychological and practical purposes. Furthermore, evaluation of student skills following the learning of examination techniques with professional patients compared with those who received training on office or clinical patients showed superior performance among the first group (10).

WHY WOMEN SHOULD ACCEPT AND ACTIVELY SEEK OUT MALE GYNECOLOGISTS

A study from the American Journal of Medicine reports that male obstetrician-gynecologists claim longer visits with female patients than do female obstetrician-gynecologists, and exhibit more patient partnership behavior, suggesting that physician behavior and medical education can be adapted to further address patient needs (11). A different study from the Johns Hopkins school of Public Health suggests that in comparison to female obstetrician-gynecologists, male ones "were more likely to check that they understood the patient through paraphrasing and interpretation and to use orientations to direct the patient through the visit [...] Male physicians expressed more concern and partnership than female physicians" (12). In fact, men might even have a heightened sensitivity about the distress that a gynecological exam can cause as they themselves have never undergone one. Something as routine as a Pap smear can be a really difficult experience for some women, and some men might go more out of their way to be gentle and explain what they're doing than female gynecologists, who may feel it's not that big of a deal because they've been through the process themselves.

Finally, between the years 1998 and 2003, male and female graduating Obs/Gyn residents were both increasingly more likely to pursue fellowship training rather than enter the general Ob/Gyn workforce, and these rates were consistently higher for men than they were for women (5). In other words, when a female patient requires gynecological tertiary care, she is more likely to be treated by a male physician and her attitudes towards this fact may impinge on the quality of care she receives. Hence, as multiple advantages of having a male gynecologist exist, our society should continue to embrace the practice of male gynecologists and further promote their positive role in the maintenance of women's health.

CONCLUSION

While the historical role of men in gynecologic procedures has been ambiguous, there is sufficient evidence in the literature today that demonstrates a gynecologist's gender is not an issue, as other characteristics of the physician, like communication and personal style take precedence. The therapeutic relationship between a woman and her gynecologist can be replete with subtleties regardless of the gynecologist's gender. While the role of gender in this therapeutic relationship remains controversial, male gynecologists continue to demonstrate an equal, and sometimes increased ability to provide high-quality care for women.

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CROSSROADS

Anthropology's Contribution to Public Health Policy Development

Dave Campbell*

Many people in the fields of medicine and public health do not understand the potential role that anthropology could play in the development of public health policy. The intention of this article is to provide readers with an understanding of the unique perspective that medical anthropology could contribute to informing public health policy decisions.

Socio-cultural anthropology has undergone significant theoretical and pragmatic changes over the past half-century. As a discipline, anthropology has been criticized for its role in imperial conquest. During colonial times, anthropologists often accompanied colonial explorers and military in order to facilitate their work, this is often referred to as 'the handmaiden era' in the history of anthropology's history. It is said that in this role, anthropologists gained the trust of natives using their linguistic proficiency and cultural awareness in order to assist the colonial state in the implementation of policies that ultimately led to further oppression and disempowerment (Pels and Salemind).

Such critiques, among others, have led to a significant redirection of anthropological thought and theory (Lewis). Social and cultural anthropology have turned towards a more critical, reflexive and holistic approach since that time. This 'reconstruction' of anthropology has resulted in an increase in criticism of those structures that had previously been assumed as 'right' and inherently 'good'. Scheper-Hughes writes about how social scientists have typically been blind to the unequal power relationships that have been harmful to informants. She calls for anthropologists to take a critical stance against such structural and institutional violence ("Coming to Our Senses").

Holism has also become an important hallmark of modern ethnography. Even the most basic concept of classic anthropology – culture – has been rethought: "the modern view of culture is to stress the importance of always seeing it within its particular context... 'culture' cannot – and should never be – considered in a vacuum" (Helman 4,7). These fundamental changes in the broad discipline of socio-cultural anthropology have manifested themselves in each of its related sub-disciplines. This paper will examine these changes in the sub-discipline of medical anthropology, and particularly how these changes allow anthropology to make a contribution to public health policy development.

RECENT EVOLUTION IN MEDICAL ANTROPOLOGY

Anthropologists have been interested in medical practices for many decades; however, medical anthropology as a distinct subfield is a relative newcomer in the world of academia. The identification of the field of medical anthropology is generally attributed to William Caudill in his paper from 1953 entitled "Applied Anthropology in Medicine" (McElroy). Since that time Medical Anthropology has established a degree of independence from its parent discipline of social and cultural anthropology. Despite this autonomy, medical anthropology's disciplinary evolution has been greatly affected by the changes in social anthropology.

Ethnomedicine was the first of the subfields of medical anthropology to develop. The premises of this ideology was that gaining an understanding of local medical beliefs and practices could be

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beneficial in the provision of biomedical services to people in cultures where biomedicine was new and unknown. McElroy states that "Since the 1940s anthropologists have helped health care providers understand cultural differences in health behaviours" (3). Emphasis on this aspect of medical anthropology led to the development of the 'Explanatory Model' framework (Kleinman) and the benchmark volume 'Clinically Applied Anthropology' (Chrisman and Maretzki) among many others. These works focused heavily on doctor-patient interaction and how anthropology can be used as a tool in biomedicine.

This thinking was followed by a new wave of thinking that parallels the turn to reflexivity in social anthropology. In 1983, the term 'critical medical anthropology' was introduced (Baer). This new brand of medical anthropology was similar to the new reflexive social anthropology in that it was critical, holistic and inward looking: "it is the work of anthropology turned in upon ourselves, our own society" (Scheper-Hughes "Three Propositions" 196). Scheper-Hughes goes on to draw explicit parallels between colonial social anthropology and clinical medical anthropology by saying that medical anthropologists played a vital role in establishing the cultural hegemony of biomedicine. She calls for medical anthropologists to break with the field of western medicine and distance themselves in order to look back upon biomedicine objectively.

ANTHROPOLOGY OF PUBLIC HEALTH

Hans Baer defines critical medical anthropology as that which "aspires to merge theory and praxis in [a] desire to promote experiential health as opposed to the functional health associated with contemporary political economics around the world" (1011). Since the emergence of critically applied medical anthropology, several anthropologists have brought this brand of anthropological enquiry to the world of public health policy.

This is not to say that medical anthropology is new to public health. Anthropologists have been involved in public health for many years. However, prior to Critical Medical Anthropology (CMA), many medical anthropologists played the role of 'cultural brokers' (Scheper-Hughes "Three Propositions"). They were often involved in mediating between populations and policy makers in much the same way in which medical anthropologists mediated between clinician and patient, or social anthropologists between colonizer and colonized. Inadvertent as it may have been, utilizing anthropology in this role in public health often inherently used techniques of "victim blaming – that is, seeing the poor health of a population as the sole result of its culture, instead of looking also at their particular economic or social situation" (Helman 5). Farmer further elaborated on this issue:

> Scholars often weaken their contributions to an understanding of infectious diseases by making "immodest claims of causality." These claims are immodest because they are wrong or misleading. They are immodest because they distract attention from the modest interventions that could treat and often enough cure people. And they are immodest because they distract attention from the preventable social disorder that exacerbates biological disorder. (5)

Clearly, there was a need for the anthropology of public health to adopt a similar perspective to that of critical medical anthropology. Van Willigen defines a dichotomy between 'anthropology in policy' and 'anthropology of policy' (164). This semantic technicality differentiates between anthropologists who assist policy makers (reminiscent of clinically applied anthropology) and those who critically appraise the work of policy makers and their policies' unintended negative effects upon the target population. Parker and Harper describe the anthropology of public health as that "which remains passionately concerned about ill-health and deprivation and the need for public policy; but also remains committed to a rigorous and critical analytical perspective" (2).

With its new critical and reflexive perspective, anthropology has a lot to contribute to the development of health policy. The field of public health – and more generally, policy development – requires research contributions from a multitude of disciplines. Williams states that "a multidisciplinary approach could best address the public health needs of a population" (Williams 1).

Public health's primary concern is to improve the health of a population. This broad-scope approach has brought epidemiology to be the most influential discipline in health policy because by using methodical sampling methods one can theoretically extrapolate conclusions about the state of health of entire populations. Turnock states that there are "five basic sciences of public health: epidemiology, biostatistics, environmental science, management sciences and behavioural sciences" (20).

It would seem that despite great anthropology's potential for informing health policy, its actual contribution is quite small – seeing that it is grouped with a half-dozen behavioural sciences as one of the five informants of policymaking. The reason for anthropology's minimized role in health policy development is likely founded in its primary methodological approach: ethnography. Thanks to an unabashed focus on individuals and small groups, many involved in the process of policymaking have argued that the data that generated by anthropological research is less valuable because it does not lend itself to broad 'scientific' extrapolation, as does epidemiological data. Ethnographic research involves observing and conducting interviews with a small group of people. With such small numbers, it is possible to argue that these individuals could easily be unrepresentative of the general population.

Despite the uphill battle that faces anthropologists in the public health sector, it is imperative to continue the work, as ethnographic inquiry has the potential to generate a great deal of rich information which can influence policy development. In the following section, I will describe four ways anthropology can influence public health policy in ways that epidemiology or other methods cannot. (A) The ability to see culture in its proper context in the social world and how culture affects all research. (B) The ability to pick up on minute and seemingly irrelevant details. (C) Independence from biomedical goals and hegemony allows medical anthropologists to add a critical voice to the public health discourse. (D) Provision of objective, qualitative data in an otherwise quantitative field.

WHAT DOES ANTHROPOLOGY BRING TO PUBLIC HEALTH POLICY DEVELOPMENT?

A – Integrated Perspective of Culture

When striving to understand disease etiology among a given population, public health specialists and human ecologists often use a 'multifactorial model of disease' (Curnow and Smith). This is a model in which there are a number of distinct factors that are thought to contribute to disease in the population. Culture is one of these factors, alongside many others, including: genetics, environment and so forth. The factorial model seems consistent with earlier medical anthropological research, relating to the method of the clinically applied anthropologist. By involving anthropologists on a clinical level it is possible to reduce the impact of the culture 'factor' on disease prevalence.

Many medical anthropologists see this model of disease as outdated and inaccurate because "it reduces the investigation of social and cultural aspects of disease to discrete, static, quantifiable 'beliefs' held by the study population" (Parker and Harper 1-2). This factorial notion of disease seems to involve the reasoning that factors of disease causation such as biology and environment are beyond the reach of culture. A modern conception of culture, as accepted by most anthropologists is significantly more complex and all-encompassing. In contemporary medical anthropology, it is believed that all research, even the most subjective and scientific, is rooted in the culture and experience of those who interpret and publish the results.

As a result of past discussions and debates within the field, contemporary medical anthropology is equipped to see beyond the established factorial model of disease. Similar discussions have taken place in medical anthropology such as those surrounding the Cartesian dualism paradigm. This is a dichotomy between the mind and the body of an individual. This worldview is characterized by a mechanistic view of disease etiology, very similar to that in the factorial model. The Cartesian paradigm continues to be used in western biomedicine and was accepted in medical anthropology for many years. Only recently, under the context of the 'new' critical version of medical anthropology, has this concept come under the microscope. Scheper-Hughes and Lock argue for the need to problematize such a seemingly simple dualism. They claim that it is not as straightforward an issue as it may seem. They challenge "medical anthropologists and clinicians to view humans and the experience of illness and suffering from an integrated perspective" (Scheper-Hughes and Lock 10).

While it may be argued that clinicians have held on to "the Cartesian Legacy," anthropologists have been working for years at developing such an integrated perspective. Medical anthropologists can contribute significantly to public health policy by providing this perspective to aid by providing an alternative to the entrenched factorial model of disease in the world of public health.

B – Holism

The new medical anthropology's "inclusion of 'the whole'" (Porter 139) is another important tool that has the potential to be of great use in policy development. Anthropology is involved in seeing the entire situation in a given community. This involves participant observation in order to capture the smallest details in the events of individuals'

lives. This also involves study of the macro-level forces and structures that are acting on people that cause them to behave the way they do.

The importance of anthropology's holism also relates to dispelling the notion of the factorial model. The factorial model sees culture in isolation from all other factors. This type of reasoning can lead to what Helman calls 'victim blaming'. The same pattern can be observed in public health policy if culture is considered isolated from political, social and economic factors. Heald provides an example from her research on HIV/AIDS policy in Botswana:

> Little money was pledged to the development of medical infrastructures… instead, a dangerously infectious disease was combated only by programmes that urged individuals to try and avoid it as best as they could in a situation where there was no means of knowing who was infected and who was not and, in the main, no way of finding out (30).

Maintaining input from an anthropological perspective is important in order to avoid this kind of counter-productive policy being developed. It is important to utilize a holistic approach to illness in order to identify all pertinent factors that contribute to a given pandemic. John Porter, an epidemiologist, has said of anthropology: "The discipline concentrates on what is actually happening and looks to 'the root' of where things come from" (Porter). Whether this 'root' at the level of social interactions between individuals, a cultural nuance or the macrocosmic structures that impact a given population, anthropological methods of investigation have proven reliable in identifying it.

C – Critical Perspective

The third feature unique to the new medical anthropology making it a valuable contributor to public health practice is its freedom from the theories and views of western biomedicine. Biomedicine, epidemiology and the other contributing sciences are inherently reductionist and hence have a very narrow scope in which to view the phenomenon of illness or epidemic. Everything is expected to have an explanation grounded in biology or 'science'.

One of the distinguishing features of the new medical anthropology is its tendency to be critical – especially of the hegemonic structure of biomedicine. Scheper-Hughes states that: "our work should be at the margins, questioning premises, and subjecting epistemologies that represent powerful, political interests to oppositional thinking" ("Three Propositions" 196). This type of oppositional thinking is important in generating new theories and in promoting necessary discourse to effectuate much needed change in public health systems.

To this day, one often hears allegations against anthropology for its past as the 'handmaiden' of colonialism. As a result of having to defend itself from these claims, the discipline has become very critical of hegemonic power structures that are involved in neo-colonial oppression of the afflicted and underprivileged. Biomedicine is a classic example of such a potentially oppressive structure. Several accounts exist that describe how "the doctor has replaced the priest as the custodian of social values" (Turner 37-38). For example, one author writes a detailed account of how the Public Health institution in the Philippines functions as an emissary of the state in subjecting people to foreign practices in order to effectuate control and domination over the public (Anderson). Anthropology's inward looking critical perspective of medicine and public health makes the data that it generates very important to the development of further policy. Scheper-Hughes states that it is "imperative to position ourselves squarely on the side of human suffering" ("Three Propositions" 196). Anthropologists have gone from being the handmaidens of colonial power to advocates for the afflicted and suffering. Many of the other sciences that contribute to health policy share biomedicine's mechanistic paradigm. Criticism is necessary to stimulate improvements in structures or programs that are already firmly entrenched. Critical medical anthropology is able to provide this unique perspective to the field of public health.

In order to remain in a good position to criticique biomedicine, it is important that anthropology maintain its distance from the biases and philosophies of western medicine. Many medical anthropologists remain critical of anthropological research that is funded by interests vested in biomedicine. This type of funding arrangement prohibits a fully critical interpretation and thus "compromises what anthropology has to offer as a discipline" (Parker and Harper 2).

D – Qualitative Analysis

The fourth significant contribution that anthropology makes to the development of public health policy is its qualitative approach to data collection. This is also unique to anthropology among all of the sciences that inform public health policy. The qualitative methodology of ethnography separates

anthropology from all of the natural sciences and many of the social sciences. Ian Hacking explains why qualitative data is so important in his critique of statistical data: "The fetishistic collection of overt statistical data about a population has as its motto 'information and control' but it would more truly be 'disinformation and mismanagement'" (280). His premise is that quantitative analysis requires extensive categorization. Many of the categories that are used are in essence constructs of the investigators and do not even exist in the worldview of the informant. This creates a false perception of reality in the minds of policymakers that cannot be avoided through structured, quantitative analysis.

A similar critique was voiced by Parker and Harper, about supposed qualitative research conducted by many traditionally quantitatively-oriented social scientists.

> Heavy reliance upon pre-designed questions, combined with spending limited periods of time in the field, inevitably structures the 'qualitative' in terms defined by the researcher rather than the researched; and this may well be at the expense of understanding the very people they seek to assist (3).

True ethnographic data strives to sidestep these misunderstandings and misrepresentations by coming to an understanding of the worldviews of its participants. This is in contrast traditional public health research, which imposes a foreign view upon informants, or counts them and in doing so categorizes them into culturally constructed groups that support the researchers' own agenda. Harper states: "one of the best ways to understand a situation is to spend extended periods of time interacting with those involved" (59). Before appropriate policy can be developed it is crucial to gain a solid understanding of the situation and more importantly, how those affected think and feel about the situation. This understanding can only be gained through ethnographic inquiry.

Porter explains the importance of qualitative ethnographic research in policy development through the use of the statistical concept of the outlier. He states that as an epidemiologist, outliers skew data in ways that don't seem to make sense. Therefore oftentimes epidemiologists will seek for rational, explainable reasons to exclude outliers from datasets. He goes on to explain that it is important to look "for ways of supporting the outlier to speak" (140). He has found that narratives derived through qualitative anthropological research methodologies allow him to discover this voice – the voice of "those who are normally unheard in the current international political climate" (139).

THE APPLICATION OF CMA TO PUBLIC HEALTH RESEARCH

Thus far, this article has sought to underscore the importance of the development of the critical perspective in medical anthropology. As has been described above, this is a crucial component of medical anthropology's contribution to public health.

Despite anthropology's strengths outlined above, a common critique of CMA is that it is overly idealized and not in line with the realities of the world. However, Peacock states that "pragmatism and searching critique need not be mutually exclusive" (12). Rylko-Bauer et al. contend that anthropology's future viability as a discipline lies in its ability to continue applying critical notions in the formulation of pragmatic solutions. They claim that "practice is part of the discipline's destiny and needs to be at the centre of discussions about anthropology's future" (187). They not only stress how important it is for anthropology to take a practical stance, but further elaborate how such is possible:

> A meaningful convergence of methodologically sound, critical, reflexive, and engaged anthropology – a convergence that builds on and learns from the extensive past experience of putting anthropology to use – will free us up to focus on differences that actually do matter in the real world. (187)

The discipline of public health is at the point of making a major decision, largely because of a publication known as the Black Report, which showed a very strong correlation between the income and health of a population (Hamlin).

> Public health remains at a crossroads. The choice is between a narrow focus on health service issues and the health problems of individuals on the one hand, or a refocus on the major underlying causes of population health on the other. (Beaglehole and Bonita 2-3)

Anthropology is well-positioned to play a key role in the informing of health policy to address these issues. This article has focused on the

changes that have occurred in medical anthropology and the anthropology of public health that allow it to be a modern and significant contributing discipline to public health policy development. Critical medical anthropology has the potential to be a great force towards informing public health policy that is focused on the macro-level underlying causes of poor health in a population. Anthropology's distinct character as integrated, critical, holistic and qualitative makes it a very potent force in encouraging public health policy in a similarly critical direction.

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CROSSROADS

The United States' Health Care Reform Bill – A Translation

Gregory Quenell*

This spring, North Americans were treated to an unusually large dose of political theater as pundits, politicians, and large mobs of protesters expressed strong opinions on the subject of Health Care Reform in the United States. After a marathon-long debate and a midnight, cliff-hanger of a vote in the U.S. House of Representatives, President Obama signed H.R. 4872, the Reconciliation Act of 2010, into law on March 23. Though the bill has been signed into law, the debate is far from over. The opinion pages of just about every newspaper in the United States resonate with calls for repeal, calls for expansion, words of optimism, prophesies of doom, and strongly-worded judgments that span every point on the political compass.

Through the countless hours of television coverage and millions of words in print, very little has been said about the contents of the bill itself. What does it say? What does it do? Health-care providers, insurance companies, large and small employers, and individuals in the United States will soon be operating under a new set of laws. What, specifically, are these laws, and what is new about them?

The text of the bill that President Obama signed on March 23 runs to some 2,300 pages. The pages are double-spaced and have wide margins, but still, the bill contains something on the order of two million words. Many of these words have little or nothing to do with health care. Among those that are relevant to health care, many amount to little more than rhetoric. But there are some parts of this bulky tome that may affect the way in which people in the United States buy their health insurance, and how health insurance companies operate in the United States.

These are the parts of H.R. 4872 that might make the bill as significant as it has been purported to be; they include new regulations on health insurance policies, new insurance "marketplaces," and a national health insurance coverage mandate.

REGULATION OF HEALTH INSURANCE COMPANIES

Some of the sections of H.R. 4872 that most directly address the weak state of the current United States health-care system are those that impose new restrictions on the practices of health insurance companies.

Starting this year, any health insurance policy that is not grandfathered will be expected to meet a set of requirements, thereby deeming it a Qualified Health Benefits Plan, or QBHP. The legislation sets minimum levels of coverage that a plan will have to provide in order to be a QBHP, and sets up a mechanism to prevent insurance companies from making excessive profits by overpricing a QBHP. (What constitutes an excessive profit, however, is left open to negotiation.)

Other parts of the new law attempt to regulate the health-insurance market so that four or five years from now, almost all available health-insurance policies will be QHBPs. It is mainly through this mechanism that the American government will try to change some of the policies and practices that have become customary among health-insurance providers. Cited below is a sampling of the rules that insurers will have to follow when offering a QHBP. Some of these rules

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will apply immediately to existing policies; others will not come into full force until 2014 or later.

An insurer will no longer be able to cancel a policy for any reason other than non-payment of premiums. Currently, it is not uncommon in the United States for an insurer to unilaterally cancel a health-insurance policy as soon as the policy holder begins asking for payments due to illness. While this business model of cost-minimization obviously benefits the insurer, it is less clear how this practice benefits the policy holder. The new law should make it more difficult for an insurer to use unilateral policy cancellation as a routine way to maximize profits.

A QBHP cannot have a lifetime limit on the amount it will pay in benefits. Insurance companies in the United States have found that setting an upper limit on the amount that can be paid out on any particular policy is an effective way to control costs and reduce risk. Holders of such policies who suffer illnesses or injuries that keep them under medical care for more than a few days have found that this practice leaves them dissatisfied.

A QBHP may not require any co-payments for preventative care or well-baby care. Co-payments for other types of care will continue, but they will be regulated. The new law attempts to keep co-payment amounts at or below thirty percent of the value of the service, with a co-payment cap of $5,000 per person per year.

Dependent children will be able to remain covered by their parents' health insurance policy until age 26. Also, children may not be denied coverage due to pre-existing conditions.

The new law will eventually make it illegal for an insurer to use a pre-existing condition as a reason to deny coverage to anyone. This, however, will not take effect until 2014 at the earliest.

The new law sets up a means by which disputed health insurance claims can be handled by a theoretically disinterested third party. Insurers will be required to allow such adjudication only for QBHPs that are purchased through the Health Exchange (described below), but the expectation seems to be that, five years from now, very few health plans will fall outside this category.

THE HEALTH EXCHANGE

Having defined a QHBP and set forth some of the rules by which insurers are expected to operate, the law goes on to define (rather abstractly) a sort of marketplace, called the Health Exchange, where insurance companies, under governmental supervision, are expected to offer QHBPs for sale. The key feature of this new marketplace is that ordinary individuals will be able to go to the Exchange and buy approved health-care plans at reasonable prices that can, at minimum, commensurate with the group rates that insurance companies charge when selling policies to large employers. (These prices are on the order of $5,000 to $10,000 per person per year.)

Currently, companies that offer health insurance in the United States are reluctant to sell policies to individuals. They prefer to sell group policies to large employers, who then include health coverage in the benefits package offered to employees. Unemployed individuals, contract-workers, or those who work part-time (for example, Wal-Mart employees with 35 hour work weeks), however, do not have access to this kind of employer-provided coverage. If such a person is going to have any health insurance at all, he has to shop for a policy on his own. Presently, this is a very difficult task. Individual health insurance policies tend to come with extravagant price tags and limited coverage. For some people, and in some whole states, they are not available at all.

Four years from now, when the Health Exchange is in place, the individual consumer will, in theory, be able to step up to the counter and compare a variety of health plans which are offered by private insurers, approved by the government, and neatly labeled and categorized as "basic," "enhanced," "premium," or "premium-plus" (or, going in the opposite order, Platinum, Gold, Silver, and Bronze). The writers of the law seem to envision a system in which all or most individual health insurance plans are sold and bought through the Health Exchange, where the government will exercise some control over both the quality and price of the product. This, however, would constitute a monopoly; therefore, the law allows for insurance companies to continue business interactions outside of the Health Exchange model. Given these circumstances, it is unclear as to why a profit-seeking insurer would choose to offer products through the more regulated Health Exchange.

An early version of the bill included a "public option," which was a sort of generic health insurance plan to be offered by the federal government through the Health Exchange. The public option would have ensured that there was at least one reasonably-priced product on the shelves at the Health Exchange. This offer would bring

customers into the Health Exchange, and their presence there might prompt private insurance companies to offer plans to compete with the public option. The Congressional compromise process, however, killed the public option early on; whatever we find on the shelves at the Health Exchange, then, (if we find anything at all) will be supplied by private insurance companies.

Of course, the Health Exchange is unlikely to have an actual counter or shelves. In fact, it's not at all clear what the Health Exchange will look like, or how consumers will interact with it. An early version of the health care bill uses a couple of hundred pages to set up a team of bureaucrats whose job will be to define just what the National Health Exchange will look like when it is finally called into existence in 2014. Since the Health Exchange does something and deals with people, it must, after all, take some concrete form in the familiar world of buildings, telephones, and websites. For the present time, though, the bill only provides a set of plans to form a development committee. And even this has mostly slipped away: before the bill was passed, further Congressional compromises eliminated the National Health Exchange and replaced it with fifty State Health Exchanges. It is now up to each of the state governments to make the initial plans to establish committees to make further plans to call forth the substance of its own particular idea of what a Health Exchange should be.

THE MANDATE

"This law will extend health care to 32 million Americans." That was the headline proclamation from the supporters of H.R. 4872 when the bill cleared its last hurdle on March 22. Currently, some 46 million Americans do not have health insurance; the new law will undoubtedly decrease that number by the brilliantly simple measure of making it illegal not to have health insurance. A section of the law with the subtitle "Individual Responsibility" (presumably the irony is unintentional) requires every American (except Native Americans and those with certain religious beliefs) to be covered by a government-approved health insurance plan or to pay a fine of up to 2.5% of annual income. Uninsured people whose annual income is less than $27,800 will pay a fine of $695, to be sure they get the message.

The new law does recognize that, among the tens of millions of Americans living without health insurance, many are doing so not out of capriciousness, but because private insurance companies either will not offer them affordable policies, or, if they happen to be high-risk individuals, will not offer them policies at all.

Health Care Reform addresses the first of these difficulties by providing "Individual Affordability Credits" - a package of subsidies and tax credits intended to ensure that, even with the new mandate, no one has to pay more than approximately 10% of his annual income to a health insurance company. For low-income Americans, the percentage paid is decreased further: those earning just above the Federal Poverty Level will be able to fulfill their individual responsibilities at a cost of no more than 3% of their annual incomes.

There are, still, those individuals who are unable to obtain any type of insurance plan. A person who is in poor health or who has an unfortunate medical history may find that no insurance company will sell him a policy at any price. It is for these people that the health care law makes its closest approach to providing public insurance. From 2010 until 2014, the federal government will offer health insurance through a temporary National High-Risk Pool. People who can document a pre-existing medical condition and who have had no health insurance coverage for six months will be eligible to buy a basic health insurance policy through this program. The out-of-pocket costs for such a policy will be capped at approximately $6,000 per year, giving it a price tag that is more or less in line with the policies that the private insurance companies offer to healthy people. The National High-Risk Pool is scheduled to disappear in 2014 because all fifty State Health Exchanges are expected to be up and running with policies for sale by this time, and even high-risk people cannot be turned away from a Health Exchange.

CONCLUSIONS

The thousands of pages of H.R. 4872 include many other changes to federal law, most (but not all) of which relate to health care. There is a section on "Additional Redistribution of Unused Residency Positions" in Medicare hospitals. Money is allocated towards a medical research institute, which, to distinguish it from ordinary research institutes, is called a "Patient-Centered Outcomes Research Institute." A whole pack of laws on college financial aid went along for the ride.

The parts of the Health Care Reform law that will most significantly affect the system of health insurance and health care in the United

States are those we've described: the attempt to regulate insurance companies, the establishment of standards for State Health Exchanges and a Qualified Health Benefits Plan, and the Individual Responsibility mandate. It remains to be seen how significant the effects of this legislation will be. Nancy Pelosi compared the creation of the Health Care Reform law to such historical milestones as the establishment of Social Security and Medicare. The large number of Americans whose health insurance is provided by their employers, however, will probably see little or no change in either their costs or benefits. The writers of the bill made a point of saying, in effect, "If you are comfortable with the plan you have, you may keep it." Insurers will have several new regulations to consider, state governments will have new bureaucracies to set up, and uninsured Americans will either have to do shop for health-care policies or pay the fines. Whether these small impositions will lead to epochal changes in health care in the United States remains to be seen.

Meanwhile, the topic of health care reform has exposed deep political divisions in the Congress as well as the general population of the United States. The rhetoric surrounding H.R. 4872, typically a cloud of hyperbole quite unrelated to the contents of the law itself, has become a favorite campaign weapon, brandished by partisans of both sides at every opportunity. Discovering the true effects of the new law will be a long and uncertain process. In the short term, most of us can sit back and enjoy watching the sparks fly whenever anyone utters the politically-charged phrase "health care reform." The sparks may not be particularly illuminating, but they do make for a good show.

CROSSROADS

An Examination of the Factors Contributing to Poor Communication Outside the Physician-Patient Sphere

Shaurya Taran*

Health care workers today acknowledge that poor communication is perhaps one of the most prevalent problems in medicine. A number of studies have looked into the causes and outcomes of poor communication in medical facilities, and it appears from these studies that the problem is pressing enough to warrant the attention of not just health care workers, but also the general public. One study conducted in the late 1990s found that poor communication was responsible for causing between 44 000 and 98 000 patient deaths annually in American hospitals alone. Other studies found that poor communication was one of the leading causes of preventable deaths in hospitals. These worrying reports have spurred a number of worldwide efforts to exhaustively characterize the factors that lead to poor communication between physicians and their patients; by contrast, there has been comparatively less emphasis on analyzing poor communication outside the sphere of physician-patient interactions. In other words, poor communication between physicians and other physicians; between physicians and nurses; and between hospitals and other hospitals, has remained largely unexplored. The relative paucity of papers in these areas is due in part to the difficulty of conducting the necessary large-scale assessments that these topics of research require. As a result, the public remains largely unaware of the few findings that have been published in the literature. It is therefore crucial that the results of these studies be brought to a larger audience so that the issue of poor communication in hospitals can be properly appreciated in all of its dimensions.

Independent authors and health care professionals including Daniel Goleman (author of the influential Emotional Intelligence) and Barbara Korsch, respectively, made some of the first pointed attempts to bring the issue of poor communication in hospitals to the public's awareness. Their work prompted general discussions in the medical community on how best to combat the problem of poor communication. Research groups began to rigorously evaluate the claim that healthy physician-patient dialogue could promote strong rapport between the two parties, while its counterpart, namely poor communication, could lead to hostility and mutual distrust between them. Today, largely because of the independent work of Goleman and Korsch, health care professionals recognize the importance of effective communication in hospitals. However, this recognition has only spurred policy changes in certain areas of healthcare; in other areas, poor communication remains as prevalent now as it did before the seminal work of Goleman and Korsch appeared in print.

One of the areas where communication can at times be deficient is in physician-physician interactions. Poor communication, when it manifests between physicians responsible for the care of the same patient, can significantly hamper medical progress. Perhaps this is not surprising, given that poor communication retards advancement in any collaborative effort; however, researchers were surprised to find just by how much poor physician-physician communication retarded progress in the treatment of patients. One important study in this area looked at communication between primary

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care physicians and subspecialty consultants. Analysts found that while almost all primary care physicians provided clear background information of their patients to consultants, a large percentage of primary care physicians failed to specify the exact reason for referral to consultants. Furthermore, only a very small percentage of primary care physicians engaged in direct contact with subspecialty consultants. Finally, a staggering percentage of consultants completely neglected to notify primary care physicians of the results of their findings (1). An important implication of these results is that the likelihood for poor communication to develop increases with the number of physicians that are involved in caring for a patient at non-overlapping stages of treatment. As it can be imagined, every poorly written, incomplete, or deficient referral poses the risk of introducing a complication into the patient's condition. In some instances these complications manifest themselves early and can therefore be easily detected and corrected; however, complications can also go unnoticed until it is simply too late to treat them. Complications of the latter type are, contrary to popular belief, quite common in medicine—which is why addressing deficient communication between physicians should be one of the primary focuses of health care policy reformists.

Another primary focus of health research groups should be on characterizing the factors involved in poor communication between residents and attending physicians. Although several papers have given compelling reasons to suggest that this issue is still quite prevalent in teaching hospitals, relatively few studies have rigorously examined the problem. One major study has, however, published its findings on the topic. This study has shown that poor communication between residents and attending physicians can often develop if residents feel that they are being pressed to perform perfectly by their supervisors. (This raises several important questions: to what extent should hospitals encourage their residents to see medical errors as tantamount to crimes? Is such a drastic policy necessary to enforce the idea that errors should be avoided at all costs? Can the same point also be made in a way that does not encourage a fear-based perfectionism? These questions, interestingly, were the focus of another paper. This paper argued that the need to function without error in fact made it much more difficult for physicians to offer high-quality care to their patients (2)). Given the unique nature of the resident-attending physician relationship, perhaps it is not surprising to see why such an area might be a likely site for communication breakdown. Although residents are instructed to ask attending physicians for advice and assistance in difficult or medically ambiguous situations, the reality is that residents oftentimes refrain from asking the appropriate questions or requesting the appropriate advice for fear of being perceived as medically incompetent. Residents may further abstain from seeking the guidance of attending physicians if they feel that they should "know" how to do something on their own. In other instances, residents simply don't wish to be a nuisance to their attending physicians (one frequently given example of this involves residents on night shifts declining to wake up their supervisors—even if they are uncertain of which course of action to take with a particular patient). Communication breakdown, and sometimes even a complete communication failure, can also result between residents and attending physicians if residents feel uncomfortable questioning the decisions of their supervisors. Oftentimes residents' hesitancy in these situations is due in part to their desire not to offend attending physicians. This fear leads to the suppression of potentially legitimate doubts and concerns on how best to handle a particular situation; as a result of the communication breakdown, patients may suffer (3).

Poor communication, as suggested by the above paper, tends to evolve out of the inevitable and irreversible hierarchy of power within hospitals. Indeed, the very existence of hierarchies in hospitals tends to increase the likelihood of poor communication developing at some level or another within the vertical power structure. This is not to suggest that the hierarchical organization of power in hospitals is a bad thing—it is only meant to imply that there are strong potentials for poor communication to develop in multiple places within the medical hierarchy. One of these places is between physicians and nurses. Indeed, just as residents feel occasionally unwilling to ask for the help of attending physicians, so too do nurses frequently refrain from asking physicians potentially "obvious" or unimportant questions (3). Given that both physicians and nurses are intimately involved in the care and support of patients, major communication breakdown between these two parties could potentially translate into serious medical difficulties for their patients. One important study found that this problem was exacerbated in certain instances, such as when physicians instructed nurses to convey important medical information to patients rather than taking on that responsibility themselves (4).

Another study showed that poor communication between physicians and nurses often developed when physicians relied on written orders to convey instructions to nurses (3). The study found that physicians routinely wrote important details into patients' medical files—often these details included crucial instructions for nurses, such as when to administer particular treatments to patients. If nurses missed checking patients' medical files, they consequently also missed the important instructions that were written in them. This raises the crucial question of why physicians continue to employ indirect modes of communication to the extent they do, and why nurses don't object to it (once again, this is not to suggest that written communication be entirely prohibited, but that written communication is, in most respects, a poor substitute for direct verbal communication). Perhaps one reason why written communication remains prevalent is that nurses fear questioning what they might consider to be a standard practice among all physicians. Here again it can be seen that the reluctance to question the practices of superiors may lead to a communication breakdown—or, more seriously, to a complete communication failure.

Just as serious as the complete failure of communication is the problem of delayed communication. Not surprisingly, delayed communication between physicians significantly hampers medical progress; for this reason, it is often classified under the broader category of poor communication. The proper orchestration of multiple events by multiple physicians depends, perhaps first and foremost, on the timely transmission of information between physicians. Instances in which this communication is delayed can often result in detrimental consequences. For example, one study found that patients were sometimes released from hospitals before all of their medical tests had even been completed (5). This particular study attributed the premature discharge of patients to delayed or ineffective communication between inpatient and outpatient physicians. Although in most cases results from pending tests were negative, in several instances pending test results were potentially actionable. For this reason, it is perhaps easy to see why timely, effective communication between inpatient and outpatient physicians is necessary at all steps in the medical process. A breakdown or delay in communication could—and, in fact, quite frequently does—lead to the development of complications in the health of patients following their premature discharge.

The challenges of finding solutions to the poor communication problem when it manifests outside the sphere of physician-patient interactions are numerous; nevertheless, several important papers have proposed some simple, practical, and occasionally innovative solutions to the problem.

Concerning poor communication between referring physicians and subspecialty consultants, one paper suggested that both parties limit indirect communication and instead engage in direct verbal communication whenever possible (1). This can be difficult (if not entirely impossible) if the two physicians belong to different clinics or hospitals. In such cases communication over telephones could be helpful; however, this is not a standard practice among physicians, and past efforts to promote telephone communication have met with little success. One recent paper proposed an interesting alternative to communicating over telephones: teleconferencing. Researchers looked into the effectiveness of teleconferencing as a means of communicating patient information; they found that physicians generally responded well to the new technology, and had little difficulty in acquainting themselves with it (6). The teleconferencing equipment itself was easy to set up and operated with a minimum of technical difficulties, which added to its appeal. Video capabilities of the teleconferencing software allowed physicians to communicate visual information, such as the results of a dermatological test, with relative ease (the quality of these images, however, was in some instances inadequate). In preliminary trials, satisfaction among first-time users of the new technology was fairly high. This study did, however, acknowledge the limitations of teleconferencing, and pointed out that such an alternative was unlikely to find its way into mainstream medicine in the near future. Other studies have provided simpler methods to increase direct communication between two physicians. One of the proposed suggestions involves creating smaller administrative units within larger hospitals to bring primary and secondary physicians into closer proximity to each other (7). If direct contact is simply not possible, such as when two physicians belong to different hospitals or clinics, then simple things such as aesthetic modifications to the referral letter format could, one study suggests, promote better communication between the two parties (7). The relatively simple nature of the above solutions suggests that it should not be difficult to increase direct communication between physicians, provided that some simple and practical modifications are made in the way that medical

information is communicated among health care professionals.

There are, however, numerous difficulties in addressing poor communication in other areas. For example, there is simply no systemized way to promote healthier communication between residents and attending physicians, or between physicians and nurses. It is perhaps easy to see why this is: Communication failures in these areas arise largely when one party fears questioning the authority or medical ability of a superior party. Hospitals have always encouraged residents and nurses to raise their concerns whenever appropriate, but the fact remains that individuals on the lower levels of the hierarchy will inevitably feel intimidated by individuals on the upper levels—which, as a consequence, causes residents and nurses to suppress instead of voice their concerns. Indeed, there is no simple solution to the poor communication problem when it manifests in the interactions of residents and attending physicians, and nurses and physicians. This could perhaps be one area of study of future papers.

Poor communication, as suggested by the collection of above studies, appears readily in interactions outside the physician-patient sphere. Given the number of places where this problem can manifest—physician-physician interactions, resident-attending physician interactions, and physician-nurse interactions, to give a few examples—it is somewhat surprising to see that poor communication in these areas received disproportionately little attention until about the mid- 1980s. Today, however, health care analysts generally acknowledge the need to completely characterize the factors contributing to poor communication when it manifests between medical workers themselves. Since this is still a relatively new undertaking, the general public remains largely unaware of the problem. Nevertheless, small initiatives can still be taken to bring the larger issue of poor communication in hospitals—with all of its grim implications and uncomfortable ramifications—into the public discourse.

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CROSSROADS

The Osler Library of the History of Medicine: McGill's Medical Memory

Christopher Lyons and David S. Crawford*

Sir William Osler bequeathed his library to McGill University in 1919; a decade later, the 8000 volumes arrived in Montreal. Then, as now, the collection consisted of primary works ("rare books"), secondary commentaries, and current works on the history of the health sciences. In the last 80 years the collection has grown considerably and the library now adds about 1,000 books to its collection yearly (mainly current publications) and receives 200 current serial titles. The Osler Library is one of the largest "history of medicine" libraries in the world and the largest of its kind in Canada. The library tries to collect current material on the history of the health sciences from all over the world and attempts to collect all medical history published in Canada. The Osler offers its resources to researchers and students through its website, publications and Research Travel Grant programme.

The librarian of today, and it will be true still more of the librarians of tomorrow, are not fiery dragons interposed between the people and the books. They are useful public servants, who manage libraries in the interest of the public... Many think still that a great reader, or a writer of books, will make an excellent librarian. This is pure fallacy.

- William Osler, (1)

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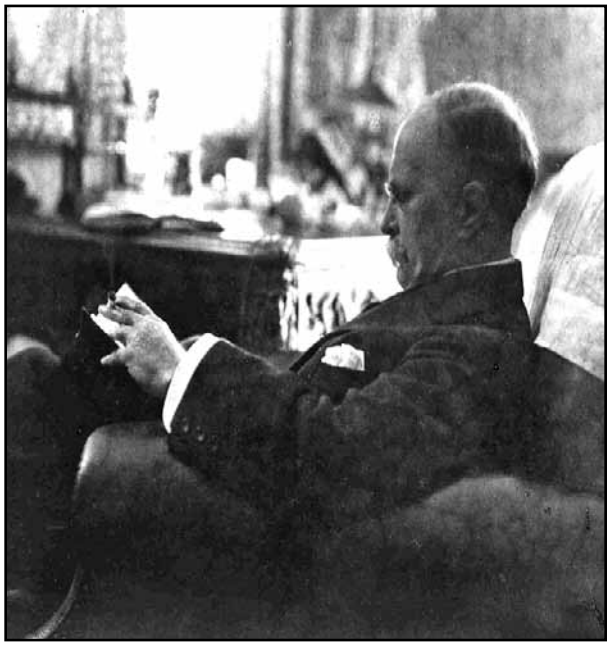

Figure 1: Sir William Osler, 1849-1919

William Osler was born in Bond Head, Canada West (now Ontario) in 1849. After commencing his education in Toronto, he became a student at McGill University in Montreal and graduated in medicine in 1872. Osler's life and career have been well described in two major biographies (2, 3). His career took him from being a professor at McGill (1874 -1884) to the University of Pennsylvania (1884 -1889), Johns Hopkins University (1889 -1905), and finally to Oxford as Regius Professor of Medicine (1905-1919) (see Figure 1).

When he died in 1919, Osler was probably the most famous doctor in the western world: apart from many articles, letters and lecture presentations, he authored and edited the textbook, Principles and Practice of Medicine. The textbook, first published in 1892, was a best seller. It went through more than eight editions and was translated into French, German, Spanish, Portuguese, Chinese and Russian (4). "Oslerian medicine" became such a great interest that "Osler Clubs" were established throughout the world. Some, such as those in the United States, London, Japan and at McGill, continue today, though now they more often discuss "history" and "Osler" rather than current medical practice.

Osler was an early proponent of the need to listen to the patient: he realised that disease and health are closely connected to living conditions. He was strongly influenced by Sir Thomas Browne, whose seventeenth century work Religio Medici, guided him throughout his career. By the time he died, Osler had been awarded a baronetcy (in 1911) and held numerous honorary degrees. Though Osler was a very serious scholar, he was also very human and enjoyed teasing and practical jokes. In his letters, speeches, and articles he comes across clearly as a person whom it would have been a pleasure to meet. Osler created a mischievous "alter ego", Egerton Yorrick Davis, under whose name a variety of letters and articles appeared on subjects ranging from the fanciful customs of the "Indian Tribes about Great Slave Lake" to vaginismus and Peyronie's Disease. Such was the notoriety of "EYD" that some medical writers continue to use this pseudonym today (5).

Osler was also a bibliophile and a strong supporter of libraries and library associations. While at McGill he served on the Faculty Library Committee; in Philadelphia, he served on the Library Committee of the College of Physicians; in Baltimore, he was a member of the Library Committee of the Medical and Chirurgical Faculty of the State of Maryland; and at Oxford, he was a Curator of the Bodleian Library. He was one of the founders and was the second President of the Association of Medical Librarians (which became the Medical Library Association) (6). He later founded and became the first and only President of the (short-lived) Association of Medical Libraries of Great Britain and Ireland (7,8). He donated books to libraries throughout his career – sometimes with such enthusiasm that he tried to donate the same book several times to the same library. For example, he attempted to donate a second original Vesalius' monumental 1543 work on anatomy De Humani Corpus Fabrica to the New York Academy of Medicine!

As expected of a bibliophile, Osler was also a book collector and, by the time he died, had assembled a personal collection of about 8,000 items. His aim was to create a library containing a record of the history of medicine and he attempted to include both primary works and secondary "commentaries". His collection included about 140 incunabula (books published before 1501); many rare primary works, such as first editions of Vesalius' de Fabrica and Harvey's de Mortu Cordis; and many commentaries and secondary works on the history of medicine. His collection also contained books showing the relationship between medicine as art, and medicine as science. In addition, the collection contained a sizable section of books on medicine in literature.

In about 1912, Osler decided to leave his library to McGill University. When he died in 1919, the whole collection, with the exception of a few items donated to other libraries, was bequeathed to McGill's Faculty of Medicine. Osler made this generous gift for several reasons: In his introduction to the catalogue, the Bibliotheca Osleriana, he wrote "as a young, untried man, McGill College offered me an opportunity to think and to work; but what is more, the members of the Medical Faculty adopted me, bore with vagaries and aggressiveness, and often gave practical expressions of sympathy with schemes which were costly and of doubtful utility" (9). Osler was also moved by pride in his Alma Mater and by "loyalty to the country of one's birth and breeding." Due to the need for a suitable space to be prepared at McGill and, more importantly, because of the need to complete the catalogue, it took ten years for the collection to reach Montreal. Osler had started to compile the catalogue before his death and it was completed in Oxford by four of

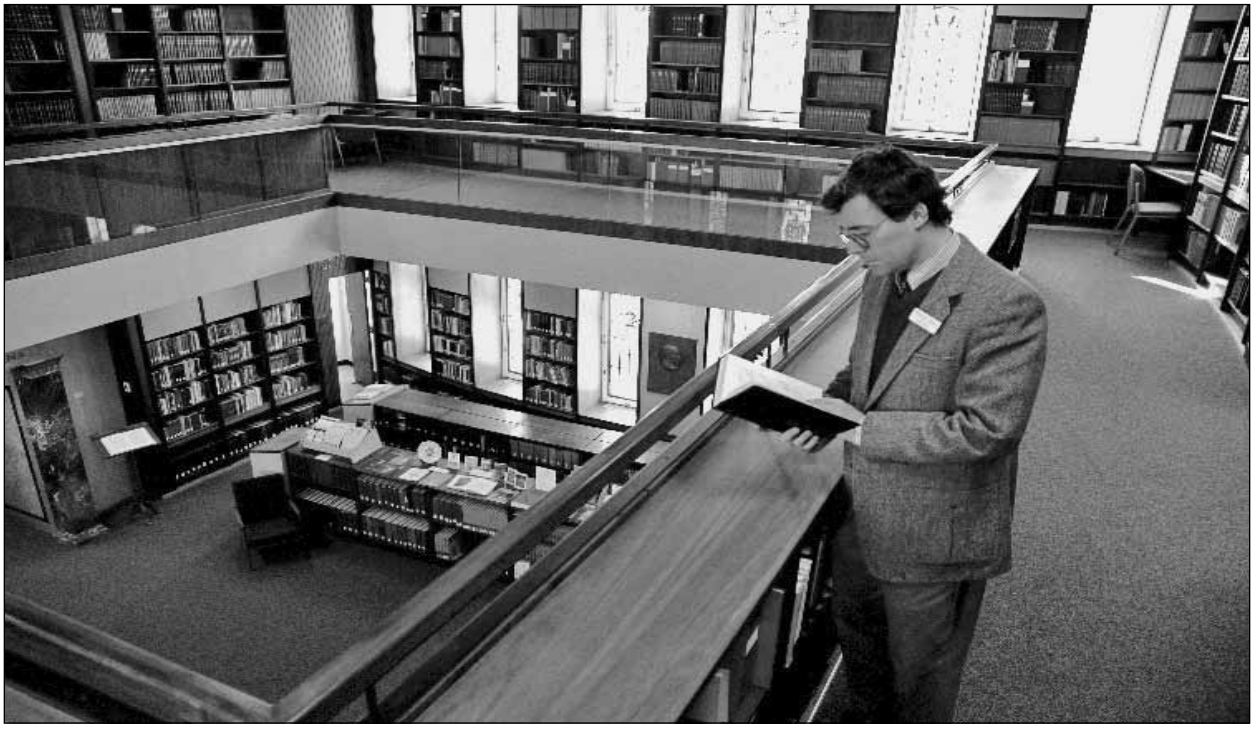

Figure 2: Mezzanine, The Osler Library of the History of Medicine

his friends (under the watchful eye of Lady Osler). This effort was led (very slowly!) by his cousin's son William Willoughby Francis. The catalogue has been described as "… probably the most complete well-annotated bibliography in the history of medicine. It reveals Osler's character better than any of his writings and stands as a monument to him," (10). The Bibliotheca was originally published in 1929 and was reprinted, with corrections and an additional prologue in 1969. It remains in-print and is available from the Library and online.

The original Osler Library was designed in the 1920s by the famous Montreal architect Percy Nobbs and built before the books arrived from Osler's home in Oxford. The original library was located in the Strathcona Medical Building, adjacent to the Medical Library. The central focus of the library (then comprising only one large room, now called the Osler Room in its current location) was a bronze plaque of Osler, under which the ashes of both Sir William and Lady Osler (who died in 1928) were placed. The library opened, amid a great deal of pomp and ceremony, in 1929 (11). In his biography of Osler the Canadian historian Michael Bliss has described the Osler Room as "a shrine, architecturally a cross between a church and a mausoleum," (3).

William Willoughby Francis, a Canadian who had a medical degree from Johns Hopkins, had been appointed Osler Librarian by McGill University in 1921 and, tellingly, often referred to himself as "Osler's Librarian". Until his death in 1959 he maintained, in the rather biting words of one commentator, "the Mecca for Osler devotees, a memorial and museum designed to perpetuate the inspiration which Osler had instilled in his followers …he kept Osler in the forefront and never allowed the Library to become anything more than Osler's Library," (12).

Osler had instructed that the library should have a Board of Curators, whose existence and composition was clearly influenced by the Curators of the Bodleian Library (13). The library did grow during the years of Francis' reign, but the meetings of the Curators were not easy, as Francis strongly resisted any attempt to expand "Osler's Library,"(14). However, by 1963, despite this resistance, the library had doubled in size to about 17,500 volumes.

Much has changed since Francis died. First, in 1964-65, the library was moved into the new McIntyre Medical Sciences Building. This was not a simple move, as it involved moving not only the library collections but also the original

Nobbs-designed Osler Room. This beautiful room was dismantled and rebuilt inside the panhandle-shaped wing adjacent to the Medical Library. This wing provided some expansion space for both the collection and the staff and allowed the creation of the Wellcome Camera (See Figure 2).

Shortly afterwards all of the pre-1851 material in the adjacent Medical Library was transferred to the Osler. The McGill Medical Library (later named the Health Sciences Library and now, the Life Sciences Library), was founded in August 1823 and is Canada's oldest medical library. The approximately 4,000 volumes transferred from it to the Osler Library added further treasures to Osler's collection (and the sale of the inevitable duplicates brought in some additional funds). The Osler Library also benefitted from the transfer of several thousand medical books published between 1850 and 1913 from remote storage. The rest of the material in remote storage, namely nineteenth and twentieth century journals and books from 1914 to 1974, were moved to open storage and are easily accessible. The extensive collection of nineteenth and twentieth-century material held at McGill in the Osler and elsewhere means that this most fecund period of medical advancement is well represented.

Francis had taught "history of medicine" at McGill and by the mid-1960s a more formal Department of the History of Medicine was established, This Department was also allocated space adjacent to the two libraries. In the mid-1970s the Osler Library and the Department were given some adjacent space and in April 1978 the Francis Wing opened. All this provided a larger rare-book area, more offices for both the library and the Department, and some additional space for the circulating collection. However, by the late 1990s this space had been more than filled and the Department had expanded (and changed its name to the Department of Social Studies of Medicine to better reflect its interests in the history, anthropology and sociology of medicine). As the close physical and intellectual links between the Osler Library and the Health Sciences Library were mutually beneficial, and it was virtually impossible to move the Nobbs-designed Osler Room again, and the decision was made to relocate the History of Medicine Department. Most of the space left vacant by this move was then allocated to the Osler Library and the whole area was renovated to provide additional shelving, better security and environmental conditions, enhanced study areas and offices. The John P. McGovern Foundation largely underwrote the cost of this major project and the newly expanded library re-opened in November 2002.

Osler's original donation had been composed of both "rare books" and current secondary works and the Bibliotheca includes several items published after Osler's death. The library now adds about 1,000 recently-published books each year (most of which are available for loan) and also acquires out-of-print or "rare books" by both donation and purchase. The library has two major collections of medical theses, about 1,100 from the University of Edinburgh (1790-1821) and about 30,000 French theses from the Université de Paris (1796-1920) (15).

The Osler Library collection now totals about 100,000 printed volumes, including the theses, and the library subscribes to approximately 200 current serials in all aspects of the history of the health sciences. As the Osler Library is a component of the McGill University Library, it benefits from McGill University's licensing of e-book and journal collections such as Early English Books Online and Early Canadiana Online and, of course, can draw on printed material in related subject areas held in other McGill libraries. The Osler is unusual for a "history of medicine collection" as it contains both rare and circulating material and is now one of the largest history of medicine libraries in the world -- certainly the largest in Canada. In addition to books and archives, the library has a small, and static, collection of medical artifacts, including one of Osler's microscopes and one of Norman Bethune's pneumothorax machines.

Information on all of the library's printed and manuscript collections is included in the McGill Library Catalogue (http://catalogue.mcgill.ca/F). As a service to students and researchers, the library has tried to make some of its reference resources available through special databases that are listed in the McGill Library Catalogue and in some cases linked to on the Osler Library's website. These include databases of the library's "reprint" and "medical almanac" collections and the Canadian Health Obituary Index (which lists nineteenth and twentieth century obituaries of health professionals). The library has quite substantial archival collections and collection-level records for most of these 150 fonds are also available in a database linked to in the Catalogue and on the Osler website (http://osler.library.mcgill.ca/archives). Most of these fonds are connected to Osler, the Osler family, McGill and Montreal medicine. Notable works include:

the papers of Wilder Penfield (the founder of the Montreal Neurological Institute) and the papers of Maude Abbott (who established what was to become the International Academy of Pathology).

The Osler Library tries to collect scholarly material on the history of the health sciences from all over the world. It has volumes in many languages, though it focuses on western European ones. The Library makes special efforts to buy any material published on the history of Canadian health sciences, including institutional histories and biographies and autobiographies of health care practitioners. (In the case of Canadian material, the Library tries to add even "non-academic" primary and secondary material.)

Medical students and practitioners may be interested in the library's collection of "pathographies" which are narratives written by patients chronicling their experiences. These are seen as a good vehicle for developing an understanding of and empathy for their patients. There are also fictional works written by doctors or which have a medical setting, such as the recent Giller Prize-winning collection of stories by Toronto emergency room doctor Vincent Lam entitled Bloodletting and Miraculous Cures,

The Osler Library currently has a staff of four: two librarians and two library assistants. It relies on the Life Sciences Library for circulation services and the McGill Library Collection Services for acquisitions and cataloguing. The Osler staff are also involved in teaching courses about the library's resources. The library has recently developed a number of student guides to the literature, available on the Library's website. The Osler Library has an active Friends group and publishes a regular Newsletter (available online at http://www.mcgill.ca/library/library-using/branches/osler-library/oslernews) as well as a series of books on medical history (Osler Library Studies in the History of Medicine). Information on these books is available on the Library website at http://www.mcgill.ca/library/library-using/branches/osler-library/shop . To assist scholars who need to use the library's resources the Library sponsors an annual Research Travel Grant to allow scholars to travel to Montreal http://www.mcgill.ca/library/library-using/branches/osler-library/grant/.

The Osler Library has also begun to digitize its special collections. Currently an online collection of photographs of Sir William, his friends and family, entitled The William Osler Photo Collection, is available (http://digital.library.mcgill.ca/osler). The library also recently launched The Marjorie Howard Futcher Photo Collection, which consists of two digitized photo albums of the daughter of former Dean of Medicine R. Palmer Howard This site shows the strong connections between the Montreal social and medical elites in the late nineteenth and early twentieth century (http://digital.library.mcgill.ca/futcher).

Although the library is no longer only "Osler's Library", it has become "The Osler Library". It continues to fulfill the aim set out by William Osler almost a century ago: to provide everyone who is interested (Canadians in particular) with a world-class collection illustrating the development of the health sciences.

DISCLOSURE

An earlier version of this article was originally published by the Journal of the Canadian Health Libraries Association/ Journal de l'Association des bibliothèques de la santé du Canada ("JCHLA/ JABSC").

A library represents the mind of its collector, his fancies and foibles, his strength and weakness, his prejudices and preferences. Particularly is this the case if to the character of a collector he adds - or tries to add- the qualities of a student who wishes to know the books and the lives of the men who wrote them. The friendships of his life, the phases of his growth, the vagaries of his mind, all are represented.

-William Osler (16)

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