Pigmaei gigantum humeris impositi plusquam ipsi gigantes vident

Students of the health sciences around the world increasingly recognize the need for new ways of learning in order to adapt to the reality of an unprecedented growth in medical knowledge. If the past twenty years have been marked by a revolution in how we access information, the next twenty may very well be gauged by how effectively we communicate this information and put it into clinical practice. We are moving beyond the information age and entering into a conceptual era where the quality of ideas is quickly becoming the new currency.

It is this theme, perhaps more than any other, which will challenge the TSMJ in the years to come. How do we become a trusted resource for students instead of a dusty, old bookend? How do we make student research more relevant to an audience saturated with information and aware of a myriad of alternative forms of communication?

If medical education must move beyond the didactic lecture, then the medical journal must, likewise, move beyond the didactic article. To this end, this year's production has focused on improving both the form and content of the journal while emphasizing new forms of medical education and the role of research as a core discipline in medicine.

Loyal readers will recognize several changes to the format of this year's TSMJ. Five clinical highlights have been added to each article, emphasizing salient points which we hope will be relevant to students working on the wards. The editorial process has also been reformed to include genuine links with the academic faculty at Trinity in order to improve the peer review process and, ultimately, the quality of our publication.

We open the journal with a look at recent research news within the Faculty of Health Sciences and present students with the unique opportunities available here at Trinity to work with world-class research groups. The role of physician as researcher is increasingly complimentary to that of clinician, and research experience is an invaluable tool that will serve students throughout their medical careers.

Our lead article on amiodarone presents an alternative form of medical education, addressing the need for critical thought and debate, rather than blind acceptance, of evidence-based medicine. The use of this medication in clinical practice highlights the tension between clinical experience and evidence-based decision making. In an age of rapidly changing protocols and unprecedented scrutiny, medical practice increasingly demands that physicians stay abreast of the latest developments in research. This new and arduous task requires equally new and creative means of making the acquisition of this information palatable and pleasurable.

The TSMJ is unique in that it is a journal run entirely by medical students, for medical students. Our strength lies in our ability to publish articles which reflect areas of medicine that students find interesting and pertinent to their development as physicians. The process of putting together the journal is, by its very nature, a learning experience. As editors, we are faced with the challenge of fostering the development of new authors while engaging the interest of our peers. It is impossible to publish all of our submissions but we are working tirelessly towards providing the maximum number of students with an opportunity to learn the skills necessary to produce an article, abstract, or poster to share with the wider health care community.

Change is in our midst. We are only beginning to realize the potential for a collaborative editorial process. We are working towards an online editing forum open to comment and discussion by all. To this end, we are beginning to improve the TSMJ website to accommodate more voices, more teaching modalities and more access to student research. If the journal is to grow it must become more inclusive and more representative of student interests. We envision a medical journal open to contributions from health science students across Ireland.

Ultimately, it is up to us to seek out and communicate the information which we feel is most relevant to our development as healthcare professionals, and it is our hope that the TSMJ will continue to be at the forefront of student led medical education.

...donec qid grandius ætas Postera sorsque ferat melior.
Robert Burton - The Anatomy of Melancholy

Jared Butler and J. David Ryan

Pharmacoeconomic Analysis of Peri-Surgical Antibiotics and Surgical Site Infections in Livingstone General Hospital, Zambia

Martin Arrigan, Brigid Halley, Peter Hughes, Leanne McMenamin, Katie O'Sullivan

5th Year Medicine

CLINICAL HIGHLIGHTS

- Multiple doses of peri-surgical antibiotics are employed prophylactically in Livingstone General Hospital, Zambia (LGH). This may reflect the practice of many third world hospitals
- The occurrence of Surgical Site Infections (SSI) in LGH is high (23%). Each SSI is associated with a considerable increase in patient stay and expenditure
- The use of prophylaxis beyond the duration of surgery is without benefit to the patient and there is evidence that doing so increases the risk of SSI
- The lack of rationale behind this strategy leads to significantly increased expenditure without proven clinical benefit in an environment of extremely limited resources
- Significant and measurable savings can be made through the development and optimisation of a prophylactic antibiotic protocol

ABSTRACT

Background: There is significant evidence to support the use of single dose surgical antibiotic prophylaxis in prevention of surgical site infections (SSI). Multiple peri-operative antibiotic doses have been observed in African hospitals by students on elective placements with unknown clinical and financial consequences. **Objective:** To investigate the use of prophylactic surgical antibiotics in Livingstone General Hospital, Zambia, in the areas of suitability, combinations, duration, cost and incidence of SSI. Furthermore, to compare these findings with evidence from the literature and current best-practice at St James's Hospital (SJH) in order to determine any possible benefits from the pharmacoeconomic optimisation of current regimes. **Methods:** A retrospective analysis of all surgical patient files from January to July, 2006. **Results:** The data gathered demonstrates a lack of prophylactic protocols and resultant ad-hoc antibiotic administration that sometimes lacked pharmacological rationale. In spite of evidence in the literature to the contrary, dosing was continued in all cases for several days. The absence of a prophylactic protocol results in increased expenditure on antibiotics without proven patient benefit and may contribute to surgical site infections with resistant organisms. The occurrence of surgical site infections was 23% and is associated with a significant cost of €133.84 per infection. In the context of limited health budgets in developing countries, this result is likely highly significant. **Conclusions:** The implementation of single dose prophylactic protocols can be expected to result in significant financial savings and may reduce the cost of treating surgical site infections. Investigation into financially feasible modifiable factors contributing to SSI would lead to significant savings and improved patient outcome.

INTRODUCTION

Livingstone General Hospital Zambia (LGH) is a 250 bed regional hospital in southwest Zambia, providing health services to 800,000 people in the area. It also trains nursing students in The Livingstone School of Nursing. Services covered include surgery, general adult medicine, paediatrics and obstetrics and gynaecology. It is staffed at any point in time by 7 to 10 doctors, three of whom are Zambian trained – of which two are qualified to consultant level – the remaining doctors come from The Ukraine (4), Egypt (1), and neighbouring African countries. The hospital also receives residents from Yale Medical School on 6-8 week tropical medicine training placements. The shortfall of qualified doctors is compensated for by 15-20 clinical officers who train for 3 years in medicine, surgery or anaesthetics and enjoy a freedom to practice which compares with that of senior house officer status, in Europe.

Financial restraints within the public health system of Zambia are severe with annual spending on essential equipment and supplies for Livingstone General Hospital at less than €12,000[1]. In this environment, rationalisation of all equipment and drugs used is essential to maximise the services that can be provided to the region.

Surgical Site Infections (SSI) are associated with significant patient morbidity and mortality as well as prolonged hospital stay and a resulting increased cost of care[2]. Rates of SSI, in African hospitals, have been found to range from 16% to 37.8%[3]. This differs from the range of reported incidences in Europe and the U.S. of between 1.5 – 20%[3,4].

This study examined the areas of SSI and peri-operative antibiotics, in LGH, from a pharmacological and economic viewpoint. The aim was to assess the pharmacological rationale of antibiotic regimes used and their economic consequences for the hospital.

METHODS

A retrospective analysis of all available surgical patient charts from January to July, 2006, was performed. Data was collected in all relevant areas including type of surgery, peri-surgical antibiotic use, the incidence of SSI, the duration of patient stay, both pre- and post-operatively, the cost of antibiotics and the cost of hospital stay, per patient, per night. A total of 63 surgeries occurred during this period, for which only 43 charts were available for analysis.

The data collected was analysed from a number of different perspectives. The combinations of antibiotics used for each type surgery (both with and without SSI), the frequency and duration of use of each combination and a comparison with SJH were summarised (Table 1). A comparison of antibiotic costs per dose between Zambia and Ireland (Table 2) was performed. Furthermore, the different expenditure on prophylactic antibiotics in LGH and St. James's Hospital (SJH) and the saving in LGH from switching to a single dose regimen were estimated (Table 3). Finally, the total overall cost associated with SSI for each type of surgery in terms of prolonged hospital stay and increased antibiotic expenditure (Table 4) was highlighted.

RESULTS AND DISCUSSION

Analysis of the results clearly demonstrates the lack of any coherent prophylactic antibiotic protocol in LGH. Across all surgical groups, both when SSI was or was not present, there was no consistency in antibiotic combinations prescribed or the duration of prophylaxis

Table 1. *Comparison of prophylactic antibiotics and number of doses used per type of surgery where no SSI is recorded and where an SSI is recorded in LGH and comparison with SJH surgical protocol.*

Surgery Type (number of surgeries with given SSI status/total number of surgeries)	Antibiotics Used in LGH (number of times combination was used) All I.V. unless otherwise indicated.	Mean number of days of prophylaxis in LGH	Antibiotic prophylaxis in St James' Hospital Prescribers Guide[5]	Number of prophylactic doses per surgery in SJH
Gastrointestinal [without SSI] (14/17)	Benzylpenicillin [QDS] (3)	3.66	Ulcer resection/Gastrectomy, Appendecomy Co-amoxiclav 1.2g IV	1
	Benzylpenicillin [QDS] + Gentamycin [TID] (5)	5.2		
	æBenzylpenicillin [QDS] + Gentamycin [TID] + Metronidazole [TID] + Other (4)*	5.5	Large Bowel Resection Co-amoxiclav 1.2g IV + Gentamycin 4mg/kg IV +Metronidazole 500mg IV	
	Other(2)†	5		
Gastrointestinal [with SSI] (3/17)	Doxycyclin po [OD] (1)	7		
	Benzylpenicillin [QDS] + Metronidazole [TID] (1)	7		
	Benzylpenicillin [QDS] + Gentamycin [TID] + Metronidazole [BD] (1)	5		
Orthopaedic [without SSI] (4/8)	æBenzylpenicillin [QDS] + Metronidazole [TID] (2)#	7	Cefuroxime 1.5g IV + Metronidazole 500mg IV	Up to 2 to 3 doses may be required
	Benzylpenicillin [QDS] + Metronidazole [TID] + Cloxacillin (1)	7		
	No antibiotic use recorded (1)	-		
Orthopaedic [with SSI] (4/8)	Benzylpenicillin [QID] + Metronidazole [TID] (3)	7.7		
	Benzylpenicillin [QID] + Metronidazole [TID] + Cloxacillin (1)	7		
Gynaecological [without SSI] (4/4)	æBenzylpenicillin [QDS] + Gentamycin [TID] (2)	3.5	Co-amoxiclav 1.2g IV	1
	Gentamycin [TID] + Metronidazole [TID] (1)	3		
	Benzylpenicillin [QDS] + Gentamycin [TID] + Metronidazole [TID] (1)	5		
Urological [without SSI] (4/7)	Benzylpenicillin [QDS] (2)	3.5	None if pre-op urine clear. If culture positive Gentamycin 120mg IV or Cefuroxime 1.5g IV	1
	Benzylpenicillin [QDS] + Metronidazole [TID]	2.5		
Urological [with SSI] (3/7)	Cefotaxime [BD] (1)	3		
	Gentamycin [TID] (1)	6		
	No antibiotic used(1)	-		

*A fourth antibiotic was added to this combination of three on two occasions. Cloxacillin QID for 4 days, Ciproflxacin BD for 6 days
† Two combinations used only once each were: Gentamycin and Metronidazole for 5 days and Amoxycillin, Metronidazole and Cirpofloxacin for 6 days.
# Cloxacillin was given to both patients who received this prophylaxis commencing 7 days post surgery for 7 and 10 day courses. There was however no SSI recorded.
æ These antibiotic combinations are used in calculations of the cost of switching to a single dose prophylactic regimen (table 3).

(Table 1). In all surgeries, patients were commenced on their prophylactic regime in the hours before surgery and continued for the number of days indicated.
Combinations of prophylactic antibiotics usually demonstrated pharmacological rationale. Occasionally, inappropriate antibiotics were used, notably, in gastrointestinal surgery where cloxacillin and doxycyclin were each used once. Furthermore, within each category of surgery the difference in prophylactic combination employed did not reflect a difference in infection risk and was without rationale (Table 1). While regular stock shortages were a significant issue for the hospital, they did not correspond with the variability from surgery to surgery and no protocols were in place for such circumstances. It is also of note that there were no culture and sensitivity facilities in LGH, and all antibiotic prescribing in the hospital was on the basis of clinical acumen.

The duration for which the prophylaxis was employed varied greatly both within and between each surgical category. In each case, prophylaxis was continued for a number of days with most patients receiving either 5 or 7 day courses (Table 1). As discussed below, this is entirely without evidence.

In comparison, current practice in SJH employs a policy of specific antibiotic prescribing of single dose duration according to surgical category, with the exception of orthopaedics which may need up to 3 doses[5].

Comparison of the cost per dose of antibiotics used peri-surgically, in LGH and SJH, reveals a large variability (Table 2). All antibiotics in LGH were less expensive, except for gentamycin, which for unknown reasons is 154% the cost in SJH. However, analysis of the total expenditure in surgical prophylaxis shows that gastrointestinal and gynaecological surgery have a 3.7-4.7 fold greater expenditure in absolute terms in LGH than SJH. Likewise, orthopaedic and urological surgery were of similar magnitude (Table 3). The increased cost of gentamycin in LGH does contribute to this difference, however, comparison of the cost of a single dose regimen in SJH with a single dose in LGH (Table 3, column 3,4) demonstrates the predominant discrepancy is the practice of using several days of surgical prophylaxis. Conversely, on a single dose basis, the costs of antibiotic prophylaxis for gastrointestinal and gynaecological surgery at SJH are 2.9 and 2.4 fold greater than in LGH. In addition, orthopaedic and urological surgery are 11.4 and 10.2 fold more expensive per dose in SJH.

Switching to a dosing regime equivalent to SJH (Table 1, column 5) would result in significant financial savings per surgery where no SSI occurs. A total savings of between €416.71 to €427.19 is estimated for the period under investigation (Table 3). This variability in savings is accounted for by the requirement of between 1 and 3 doses of antibiotics in orthopaedic surgery in SJH.

The overall incidence of SSI in LGH was 23% and varied

Table 2. *Comparison of Antibiotic cost per dose in LGH and SJH*

Antibiotic	Antibiotic Cost per dose in Zambia (1)	Antibiotic Cost per dose in Ireland (6)	Cost of drug per dose in Zambia as a % of that in Ireland
Benzylpenicillin (1megaunit)	€0.37	€0.60	62%
Gentamycin (80mg/2ml)	€0.86	€0.56	154%
Metronidazole (500mg/100ml IV)	€0.57	€06.16	9%
Amoxycillin (125mg/ml)	€01.43	€2.29	62%
Cloxacillin (500mg/50ml)	€0.02	- †	- †
Ciprofloxacin (2mg/ml.50ml vial)	€1.26	€16.37	7.7%
Cefotaxime (500mg IV)	€02.86	€3.34	8.6%
Doxycyclin po (course of 8 tabs)	€0.11	€4.69	2.3%

This table compares the cost of all antibiotics recorded in the study regardless of the pharmacological rationale for their use.
† Other anti-staphylococcal penicillins are used in Ireland. No price was available for cloxacillin and thus no price comparison made.

Table 3. *Expenditure on antibiotic prophylaxis per surgery in LGH compared with SJH where no SSI occurs. Column 4 shows savings per surgery from switching to a dosing regimen equivalent to SJH*

Surgery Type	Mean prophylactic antibiotic expenditure per surgery in LGH	Mean prophylactic antibiotic expenditure per surgery in SJH	Predicted cost per surgery of switching to a single dosing regime as per SJH‡	Predicted saving per surgery from switching to a single dosing regime as per SJH‡
Gastrointestinal	€23.17	€6.23*	€2.17	€21.00
Orthopaedic	€12.89	€14.89 - €47.67	€1.31 - €3.93	€8.96 - €11.58
Gynaecological	€17.89	€3.84	€1.60	€16.29
Urological	€6.29	€8.73	€0.86	€5.43

*Prophylaxis in GI surgery in SJH varies according to the extent of the surgery. This figure is the mean expenditure per surgery that would have occurred had SJH encountered the same GI procedures as LGH.
‡Dosing regimen in SJH is single dose except for orthopaedic where 2-3 doses may be required. Agents used in calculations were chosen to maintain the spectrum of activity in SJH presrcribers guide (see Table 1 marked æ).Gentamycin is used for urological procedures.

from 0% for gynaecological to 50% for orthopaedic. This figure lies within the range found in other African studies[3].

The occurrence of SSI were associated with an average increase in pre- and post-operative hospital stay of 6.8 and 10.5 days respectively, and also increased antibiotic usage. A wide range and standard deviation for both pre- and post-operative hospital stay was found (Table 4).

The average increase in cost per SSI was €131.84 (Table 4). This figure takes into account the increased post-operative hospital stay and increased cost of antibiotic usage as a result of infection. It does not account for the any increased pre-operative stay, as this is not incurred as a result of the infection. The total cost of all SSIs during the period examined was €1318.40, a significant sum in the context of the extremely limited hospital budget.

The availability of patient charts was limited to 43 of the 63 surgeries in the period under investigation. This was attributed to general administrative problems and issues of inadequate record keeping in an environment of limited resources. However, it is notable that no deaths were recorded in any of the files available. Data on the incidence of death from SSI in Africa is unpublished [7] and it is therefore impossible to make any inferences or conclusions about the significance of unavailable files.
It is of further note that the comparison made with SJH is based entirely on protocols outlined in SJH Prescriber's Guide rather than an actual comparison with prophylactic antibiotics used in practice. A future study on the level of compliance with SJH guidelines is needed to make a realistic comparison between SJH and LGH, along with the appropriateness of calculating cost savings on the basis of these prescribing practices.

An investigation into prophylactic surgical antibiotic use by Harbrath et al.[8] concluded that only one dosage of antibiotic pre-operatively is of benefit to the patient, unless the surgery is longer than three hours. For surgeries longer than 3 hours, a second dose is the most effective way to maintain antibiotic levels in the desired range. Twenty minutes pre-incision is the optimal time for administration of the antibiotic. Alternatively, in long surgeries, single preoperative doses of extended half-life antibiotics were as effective as a two-dose regimen in preventing wound infection and have been shown to be more cost effective than multiple-dose regimens[9].

There is no evidence of benefits in extending antibiotic administration beyond the completion of surgery. Furthermore, the practice of multiple post-operative doses has been found to increase the incidence of antibiotic resistant bacteria in SSIs that do occur and, therefore, increases the risks to the patient[8,10,11].

The most significant factor influencing the healing of surgical wounds and subsequent development of SSI is the level of bacterial burden at the incision site[12,13,14]. The primary source of this contamination has been found to be the skin[15]. Preoperative skin preparation with chlorhexidine has been found to reduce the bacterial count on skin by 80%-90%, though it has not been possible to correlate this directly with a corresponding reduction in SSI incidence[16]. Prolonged skin preparation may release organisms from deeper layers[16].

The risk of SSI infection has been found to increase with the length of time between shaving the site for surgery and commencement of surgery[13]. In a study of clean wound

Table 4. *Incidence of SSI, associated increase in hospital stay, antibiotics usage and overall expenditure*

Types of Surgery	Total Number	Number of SSI	Mean pre-op stay per SSI (days) (range)	Mean post-op stay per SSI (days) (range)	Mean increase in cost of antibiotic treatment per SSI*	Total additional cost incurred per SSI#
Gastrointestinal	17	3	17.3 (7-24)	14.3 (7-28)	€26.84	€126.58
Orthopaedic	8	4	8.25 (0-15)	14 (5-27)	€12.78	€109.23
Gynaecological	4	0	-	-	-	-
Urological	7	3	10.3 (1-24)	19.3 (11-26)	€12.00	€166.53
Otheræ	7	0	-	-	-	-
Total SSI	43	10	11.6 (0-24) SD = 9.25	15.7 (5-28) SD = 8.89	€16.76	€131.84
Total for no SSI§	43	33§	4.8 (0-20) SD = 4.82	5.2 (0-16) SD = 4.01	-	-

The average pre-op stay with no SSI was 4.8 days, The average post-op stay with no SSI was 5.2 days. *This figure is the average expenditure on antibiotics including prophylaxis per SSI minus the average expenditure on antibiotic prophylaxis in those who do not get an SSI. #Total additional cost = Cost of increased post-op stay compared with no SSI + Increased expenditure on antibiotics due to SSI. The cost per patient per night in LGH was €10.96. æSurgeries in the 'other' category were due to trauma(4), thyroid cyst(1), cleft palate(1) and lumpectomy(1). §This row is for comparison with Total SSI row. Data fits in the same columns as with SSI columns except for entry number 3 which is the number of surgeries without SSI (33).

SSIs, shaving more than two hours prior to the surgery was found to be associated with an SSI rate of 2.3%, in comparison to trimming of body hair which was associated with an SSI rate of 1.7%[14].

The abrasive action of shaving on the skin is the most likely reason for this and essential shaving should be carried out as close to the time of surgery as possible[14].

It is important to note that good infection control is multi-factorial and dependant on suitable infrastructure, equipment, clean rooms and appropriate training for staff. In developing countries, many of these factors cannot currently be altered without massive investment and thus key areas of intervention are limited.

CONCLUSION

Surgical antibiotic prophylaxis in LGH was highly variable and reflected the lack of protocols in this area. As a result, the prophylaxis used varied greatly between patients and sometimes lost rationale. Without exception, prophylaxis continued for several days, contrary to clinical evidence. The continuation of antibiotic dosing beyond the end of surgery is associated with increased expenditure on antibiotics of over €400 for the period in question. There is also strong evidence in the literature to suggest that this may be a contributory factor to SSIs with resistant organisms. The combined increase in antibiotic expenditures for the files available was €1730. Extrapolation of this figure to the entire year for all patients undergoing surgery would result in an annual cost of over €4,300, though it should be noted that the reason for limited chart availability is unknown and the real cost could be higher.

The implementation of an evidence-based prophylactic antibiotic protocol at LGH would likely result in significant savings on antibiotic expenditure without increasing risk to patients. Such a protocol might also reduce the cost associated with treating those SSI that occur due to resistant organisms. It should be noted that without culture and sensitivity screening at LGH, such a protocol would be impossible to develop. However, switching to a single prophylactic pre-operative dosage strategy should be given serious consideration. This straightforward change in practice would results in significant cost reduction and may reduce the development of resistant pathogens.

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Chest Pain In a Previously Healthy Young Male: Possible Cocaine-Induced Vasospasm?

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5th Year Medicine

CLINICAL POINTS

- When taking a history of chest pain always enquire about smoking status (pack years), presence/absence of diabetes mellitus, hypercholesterolaemia, hypertension, and whether there is a previous history of cardiac disease
- In any pain history enquire about: site, onset, character, radiation, associated features, timing, relieving/aggravating factors and severity
- When a patient presents with chest pain an ECG, a chest x-ray and cardiac troponins must be ordered
- Always consider the possibility of cocaine use in a young patient presenting with chest pain in the absence of risk factors regardless of professional or social status

Patient X, a 22 year old Caucasian male presented to St James Hospital (SJH), Dublin complaining of `unbearable` central chest pain that began 1 day prior to presentation.

History of The Presenting Complaint: X described a central, retrosternal pain that was constant, dull and crushing in character with a superimposed, intermittent and stabbing element. The pain began 1 day prior to presentation. It radiated to the upper pectoral region, but not to the jaw or left arm. There was no associated nausea, sweating or vomiting. The pain was aggravated by inspiration and movement, and was not relieved by simple analgesia. X graded the pain as 7/10 but graded the intermittent, stabbing element as 10/10. X denied any previous episodes of similar chest pain. After much initial denial, X eventually admitted to cocaine use on the evening prior to the onset of pain. Following physical exertion on the following afternoon, he developed the chest pain. He thought the pain would resolve spontaneously but when it failed to do so he became concerned and attended the emergency department at SJH.

Past Medical History: X has no previous medical history of note and has had no prior admissions to hospital.

Past Surgical History: X has no surgical history of note.

Medications: X does not take medications regularly and he has no known drug allergies.

Family History: X has a positive family history of cardiac disease.

Social History: X is married and is a banker, working in Dublin. He is a smoker of 15/day for 2 years, he admits to cocaine use once a month, a habit he began 5 months prior to presentation. He is a social drinker (approximately 18units/week).

Review of Systems: Musculoskeletal - X described a feeling of tenderness over the left pectoral region which is exacerbated by movement.

On Examination: X appeared alert and orientated in person, time and place. He was not in any significant discomfort but was notably agitated and anxious. His vital signs were normal (BP 127/85mmHg, Heart-rate 73bpm, temperature 36^{o}C, respiratory rate 12/minute and O_2 saturation 99% on room air).

Respiratory Exam: X complained of pain over the left pectoral region on movement (sitting forward) and on inspiration. His lungs were clear to percussion and auscultation.

Cardiac Exam: The JVP was not elevated and there was no ankle oedema. The apex beat was not displaced and no thrills or heaves were evident on palpation. Heart sounds 1 and 2 were present; with no added sounds and no murmurs.

Gastrointestinal Exam: The abdomen was soft, non tender and not distended. There was no evidence of hepatomegaly or splenomegaly. Bowel sounds were present on auscultation.

Nervous System Exam: The pupils were equal and reactive to light and accommodation. Cranial nerves 2 to 12 were intact. The peripheral nervous system exam was normal.

Musculoskeletal Exam: There was tenderness to palpation over the left pectoral region. This was exacerbated by inspiration and on adduction and internal rotation of the left arm.

Impression:
1. Cocaine-induced coronary vasospasm
2. Musculoskeletal pain
3. Pericarditis

PLAN

1. 12 lead ECG
2. IV access and bloods (full blood count, renal profile, liver function tests, coagulation screen, toxicology and cardiac troponins)
3. Analgesia (2.5mg morphine iv)
4. Aspirin (300mg), clopidogrel (300mg) and sublingual GTN (2 puffs)
5. Chest X ray

RESULTS

1. ECG - Normal sinus rhythm, T wave inversion in V1, no other abnormalities detected.
2. Chest X-ray - normal.
3. Bloods - normal troponin level (<0.01), normal D-dimer (171.3), negative toxicology.

CONCLUSION

X had chest pain suggestive of an acute coronary syndrome in the absence of a definite acute myocardial infarction (MI), ischaemic ECG changes or a positive troponin level, thus he was considered to be a suitable candidate for the chest pain assessment unit (CPAU).

X was admitted to the CPAU 4 hours after presentation, where he was monitored by 12 lead ECG for 24 hours and had 3 CK-MB levels taken during this period. Because there were no abnormalities detected in the ECG or CK-MB levels during this period, X was considered suitable for an exercise stress test (EST). The EST revealed an appropriate heart rate and blood pressure response to exercise and X managed 13.32 minutes of exercise according to the Bruce Protocol before the test was stopped due to chest discomfort. The chest discomfort resolved 2 minutes into recovery and the EST was considered normal.

X was discharged from the CPAU on the following day and given an appointment to attend the nurse specialist led review clinic 48 hours post discharge.

X attended the review clinic as scheduled. He was strongly advised to discontinue cocaine use and to abstain from cigarette smoking.

X was discharged to the care of his GP and advised to return to the emergency department should any similar episodes of chest pain occur.

DISCUSSION

Cocaine is the second most common illicit drug used and the most frequent cause of drug related deaths in the United States[1]. The younger age group, 18 - 25 years, are the most common users and it is estimated that 11% of the population have used cocaine at some point[1]. Cocaine may be smoked, inhaled or injected. Its use is associated with both acute and chronic complications that may involve any system, the most common being the cardiovascular system (Table 1)[2]. Cocaine use should be considered as a differential diagnosis in any young adult with a cardiovascular event because of its potential to cause serious cardiovascular and cerebrovascular

Table 1: Cocaine related complications

SYSTEM	COMPLICATIONS
Cardiovascular	myocardial ischaemia, coronary artery spasm, acute MI, atherosclerosis, myocarditis, arrhythmia, hypertension, cardiomyopathy and endocarditis[2]
Neurological	intracranial haemorrhage, cerebral infarction, seizures and migraine[3]
Vascular	aortic dissection, rupture and vasculitis[4]
Gastrointestinal	Mesenteric ischaemia, infarction and perforation[5]
Respiratory	pulmonary oedema, infarction and haemoptysis[6]
Musculoskeletal and dermatological	rhabdomyolysis, skin ischaemia, superficial/deep venous thrombosis and thrombophlebitis[7]
Genitourinary and obstetric	renal and testicular infarction, abruptio placentae, spontaneous abortion, prematurity and growth retardation[8]

and cercomplications. Among the cardiac complications, myocardial ischaemia and infarction have been most commonly reported in clinical and autopsy studies[2]. Complications can follow any route of administration. Pre-existent vascular disease is not a prerequisite for the development of cocaine-related cardiovascular complications[2].

Pharmacology of Cocaine

Cocaine (benzoylmethylecgonine) is an alkaloid extract from the leaf of the Erythroxylon coca plant, which usually grows in South America[1]. Cocaine is available in two forms:

1. Hydrochloride salt: This can be taken orally, intranasally or intravenously.
2. Free base: Known as crack cocaine. It can be smoked and is considered to be the most potent and addictive form.

Cocaine is absorbed in both forms from all body mucous membranes. The peak effect ranges from 1 to 90 minutes depending on the route of administration. The half-life ranges from 0 minutes after inhalation to 2-3 hours after gastrointestinal ingestion, with duration of action between 15 minutes by IV or inhalation routes to 3 hours by the gastrointestinal route[2].

Mechanism of Action

Cocaine acts as a powerful sympathomimetic agent. It blocks the re-uptake of dopamine and noradrenaline producing high levels of these neurotransmitters at the postsynaptic receptors. Cocaine blocks sodium channels, which accounts for its local anaesthetic effects. It also produces a dose dependent increase in blood pressure and heart rate. By blocking the reuptake of dopamine, cocaine causes euphoria; and by blocking noradrenaline re-uptake vasoconstriction results. Coronary artery spasm is exacerbated by beta blockade and antagonized by phentolamine, suggesting that it is mediated through the stimulation of alpha adrenergic receptors[2].

Cocaine-Related Chest Pain and MI

The commonest cocaine related cardiovascular problem is chest pain. MI after cocaine use involves several mechanisms. It is related to the block of the re-uptake of noradrenaline that leads to alpha and beta adrenergic effects. These include increased heart rate and blood pressure, and simultaneous coronary vasospasm, with reduced myocardial oxygen delivery leading to ischaemia. In addition, there is evidence that cocaine activates platelets, increases platelet aggregability, and potentiates thromboxane production thereby promoting thrombus formation. Acute coronary events and MI can occur minutes after cocaine administration or as late as a few days afterwards. However, the highest risk of coronary events is in the first hour after cocaine use with no relation to the dose or route of administration[2].

Cocaine-induced MI often occurs in patients with normal coronary arteries, and the typical patient is described as a male in his 30s, with only smoking as a coronary risk factor; 50% of these patients would have experienced chest pain previously. The anterior wall is involved in most cases (77%) of cocaine induced MI[2].

Chest pain and ECG changes are very common in cocaine users, even in the absence of myocardial ischaemia and MI, and only 6% of cocaine-induced chest pain is attributable to MI. The risk of MI is increased up to 24 times over baseline in the first 60 minutes after cocaine use[2]. Young patients presenting with chest pain and suspected acute coronary syndrome should be questioned about cocaine use. Cocaine-induced MI can be difficult to diagnose accurately, as the ECG is difficult to interpret in young patients. Furthermore, MI can occur with normal ECGs or with only non-specific findings. Serum creatine kinase is not a reliable indicator of myocardial injury and is increased in almost half of cocaine users without MI; this is thought to be attributable to rhabdomyolysis. In contrast, cardiac troponins are more sensitive and specific for myocardial injury and should be used for the diagnosis of MI[2]. Fortunately, there is a low incidence of complications after cocaine-induced MI. This is possibly due to the young age of most patients, who often have normal coronary arteries and these complications mostly occur within 12 hours of presentation. Ventricular arrhythmias occur in 4% to 17%, congestive heart failure in 5% to 7%, and death in less than 2%[2].

Stroke

The risk of stroke is considerably increased with cocaine use[3]. The aetiology of cocaine-induced brain ischaemia is multi-factorial:

1. Cocaine stimulates vasospasm, presumably by increasing levels of extracellular monoamines, particularly dopamine.
2. Cocaine may cause thrombus formation in the cerebral vasculature.
3. Long - term cocaine use may cause a cerebral vasculitis that impairs cellular oxygenation by exacerbating non-laminar blood flow and sludging in the vessels, with consequent increase in platelet aggregation and thrombus formation.

Over time, repeated ischaemic episodes and subsequent reperfusion can weaken vessel walls, thereby increasing the likelihood of cerebral haemorrhage[3].

Management of Cocaine Related Chest Pain

The cornerstone of treatment is sedation using benzodiazepines, which decrease central sympathetic outflow[9].

In addition:

1. Hyperthermic patients should be cooled
2. Fluid resuscitation must be initiated to maintain urine output

3. Seizures, if present, should be treated with benzodiazepines
4. An urgent CT brain should be ordered in all cases of seizures (to exclude an intracranial haemorrhage)
5. Acute MI should be excluded using cardiac troponins in patients presenting with chest pain
6. Myocardial ischaemia should be treated with aspirin, benzodiazepines or nitrates, heparin, and opiates
7. Beta blockers alone are absolutely contraindicated (they cause unopposed alpha stimulation which worsens coronary and peripheral vasoconstriction)

CONCLUSION

The recognition of cocaine induced ischaemia or MI is crucial for optimal management. A previously healthy young person presenting with cardiac type chest pain should be asked about cocaine, or any illicit drug, use. Many cocaine users have little or no idea of the risks associated with its abuse. Patients, health care professionals, and the public should be educated about the dangers and the considerable risks of cocaine and other illicit drug use.

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Peripheral Nerve Injury and Repair

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Clinical Points

- Degradation and regeneration of peripheral nerves is distinct from that of nerves in the central nervous system
- Prognosis of peripheral nerve injury is dependant upon age, the nerve injured, the level of the injury, the degree of injury and the timing of repair
- A sophisticated degradation process occurs following injury, before regeneration of a nerve can take place
- Management of peripheral nerve injuries has remained largely unchanged over the last century
- Management of peripheral nerve injuries requires a multi-disciplinary team

ABSTRACT

Peripheral nerve injury can be devastating for a patient. A host of factors influence the highly dynamic degenerative processes that ensue. This article introduces some fundamentals of the mechanisms involved and current treatments available. It serves to highlight some of the more important aspects of the highly sophisticated processes that underlie the pathophysiology of injury and recovery. As will be seen, the regenerative capacity of peripheral nerves is remarkable. Hopefully, a better understanding of the regenerative processes involved will one day assist in the development of new therapies to treat central nervous injury.

Anatomy of the peripheral nerves - General Features

It is essential for clinicians to have an understanding of basic anatomy in order to classify and subsequently treat a nerve injury. The cells of the nervous system vary more than those in any part of the body[1].

The peripheral nerves comprise the cranial and spinal nerves linking the brain and the spinal cord to the peripheral tissues. There are 31 pairs of spinal nerves which contain a mixture of sensory and motor fibres. They are formed by fusion of anterior and posterior nerve roots. The posterior rami of the spinal nerves generally supply the erector spinae muscles and skin of the trunk, whilst the anterior rami innervate the limbs together with the muscles and skin of the anterior part of the trunk. The anterior rami supplying the upper and lower limbs are redistributed within brachial and lumbosacral plexuses respectively.

There are 12 pairs of cranial nerves which are concerned with receiving information and controlling activities of the head and neck and, to a lesser extent, the thoracic and abdominal viscera. Unlike spinal nerves, only some are mixed in function and so carry both motor and sensory fibres. Others are purely motor or sensory e.g. the olfactory nerve is purely sensory.

Microscopic structure

Peripheral nerve fibres have been classified in relation to their conduction velocity, which, in general is proportional to size and function. Group A consist of fibres up to 20μm in diameter (subdivided into α, β, γ and δ), Group B up to 3μm in diameter, and Group C up to 2μm in diameter. The widest fibres appear to conduct most rapidly. However, it is not possible to make a precise estimation of function from mere size. The largest myelinated fibres may be motor or proprioceptive, and the smallest, whether myelinated or not, are autonomic or sensory[2]. However it is not possible to designate individual fibres on the basis of structural features alone[3].

Within a given peripheral nerve, fibres are organised in separate bundles known as fascicles. Less than half of the nerves are enclosed within myelin sheaths. The remaining unmyelinated fibres travel in deep gutters along the surface of Schwann cells. Each Schwann cell is surrounded by a network of reticular collagenous fibres, the endoneurium. Each fascicle is covered by an epithelium, the perineurium. All of the fascicles are surrounded by epineurium (a loose vascular tissue) which encloses an individual nerve.

Generally regional arteries supply nerves by a series of longitudinal branches which anastomose freely within epineurium, so that nerves can be displaced widely from their beds without risk to their blood supply.

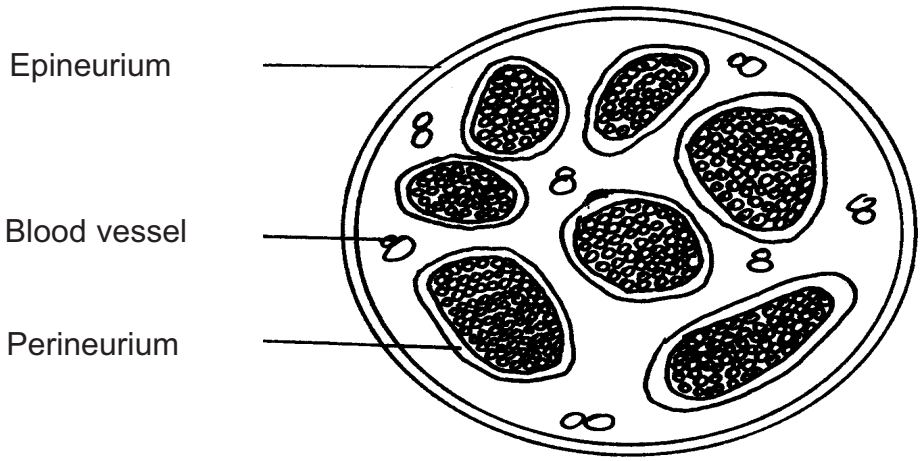

Figure 1. Schematic representation of a cross-section of a typical individual nerve fibre.

Classification of Nerve Injury

To help clinicians grade the degree of injury to a peripheral nerve, various systems have been developed which correlate microscopic changes after injury with symptoms of the patient. These systems can give a fairly accurate prognosis of a particular injury type. The two systems used most widely are those developed by Seddon [4] and by Sunderland [5].

Seddon's classification, which is used more frequently in a clinical setting than Sunderland's, consists of three terms to describe injury to a peripheral nerve. Ranging from least to most severe these are: neuropraxia, axonotmesis and neurotmesis. Neuropraxia is a mild form of injury. Here, there is little or no structural damage with no loss of nerve continuity. Symptoms are transient and most likely due to an ion-induced conduction block, thought to result from a mixture of mechanical compression and ischaemia. There is no severance or tearing of the neural elements and there is little or no histological change seen. The effects appear to be reversible, unless ischaemia persists for approximately 8 hours. Examples of this type of injury include entrapment neuropathies, such as carpal tunnel syndrome, and Saturday night palsy, a radial nerve paralysis caused by pressure on the arm after the person has fallen asleep, usually during an alcoholic binge. There is excellent recovery from neuropraxia, normally within weeks or months. Axonotmesis is the term used when there is complete interruption of the nerve axon and its myelin sheath, but the mesenchymal structures including perineurium and epineurium are either completely or partially intact. This type of injury may be seen in isolation, as with a birth-related brachial plexus injury, or in association with fractures such as a radial nerve injury secondary to a humeral fracture. Lacerations, including those caused by broken glass, are also a common type of injury that may cause axonotmesis. Whereas these can be complete transections, usually some element of nerve continuity remains[6]. Most research involves lacerating animal nerves as this type of injury may be easily reproduced. Therefore, a large proportion of our knowledge on peripheral nerve injuries is represented by this injury type. Prognosis for axonotmesis depends on the extent of injury, with increasing severity related to poorer outcome. Neurotmesis occurs when a nerve, along with its surrounding stroma, becomes completely disconnected. There is no spontaneous recovery and even after surgery prognosis is poor. This type of injury is only seen in major trauma.

Sunderland's classification differs from Seddon's in that five different classes are used. First degree injuries are equivalent to neuropraxia. 2nd, 3rd and 4th degree injuries are equivalent to axonotmesis, the difference being the degree of mesenchymal damage to the nerve. In 2nd degree injuries recovery is good whilst in 4th degree injuries recovery is poor. Fifth degree injuries are equivalent to neurotmesis.

Reponse of Neural tissue to Injury- Degradation and Degeneration

Degradation in the distal segment

In the mildest form of injury (neuropraxia) there is no histological change in the nerve fibre and full recovery is expected. This is also the case for 2nd degree injuries, the mildest form of axonotmesis. In the more severe cases of injury, an active Ca^{2+} mediated process- known as Wallerian degeneration, takes place distal to the lesion[7].

Within hours of injury, myelin and axons break up to form ellipsoids. By 48 to 96 hours after injury, axonal continuity is lost and conduction of impulses no longer occurs. Degradation of the myelin and axons occurs due to a Ca^{2+} activated release of proteases by Schwann cells. The Schwann cells are of vital importance in Wallerian degeneration, as they rapidly divide into daughter cells that up-regulate gene expression for

molecules to assist in both the degeneration and regeneration processes. The Schwann cells also work in conjunction with macrophages, supplying them with cell debris to engulf and remove. There is a co-dependence between these cells as the macrophages are mitogenic to Schwann cells and participate with Schwann cells in the provision of trophic (feeding) and tropic (guidance) factors for regenerating axons. Obviously, there are a number of mediators that play a role in Wallerian degeneration. These mediators include serotonin and histamine released by mast cells which enhance macrophage migration and are also therefore pivotal in the process. It is possible other mediators may be involved but have yet to be discovered.

The end result of the dynamic Wallerian degeneration is a shrunken nerve skeleton with intact connective tissue and perineural sheaths and multiplying Schwann cells. In more severe injuries the process is complicated by vigorous inflammation and oedema. Fibroblasts proliferate and a dense fibrous scar causes a fusiform swelling of the injured segment. In 4th and 5th degree injuries, many axons form whorls within the scar tissue, or are turned back along the proximal segment or into the surrounding tissue. These factors all reduce the likelihood of regenerating axons reaching the proximal stump.

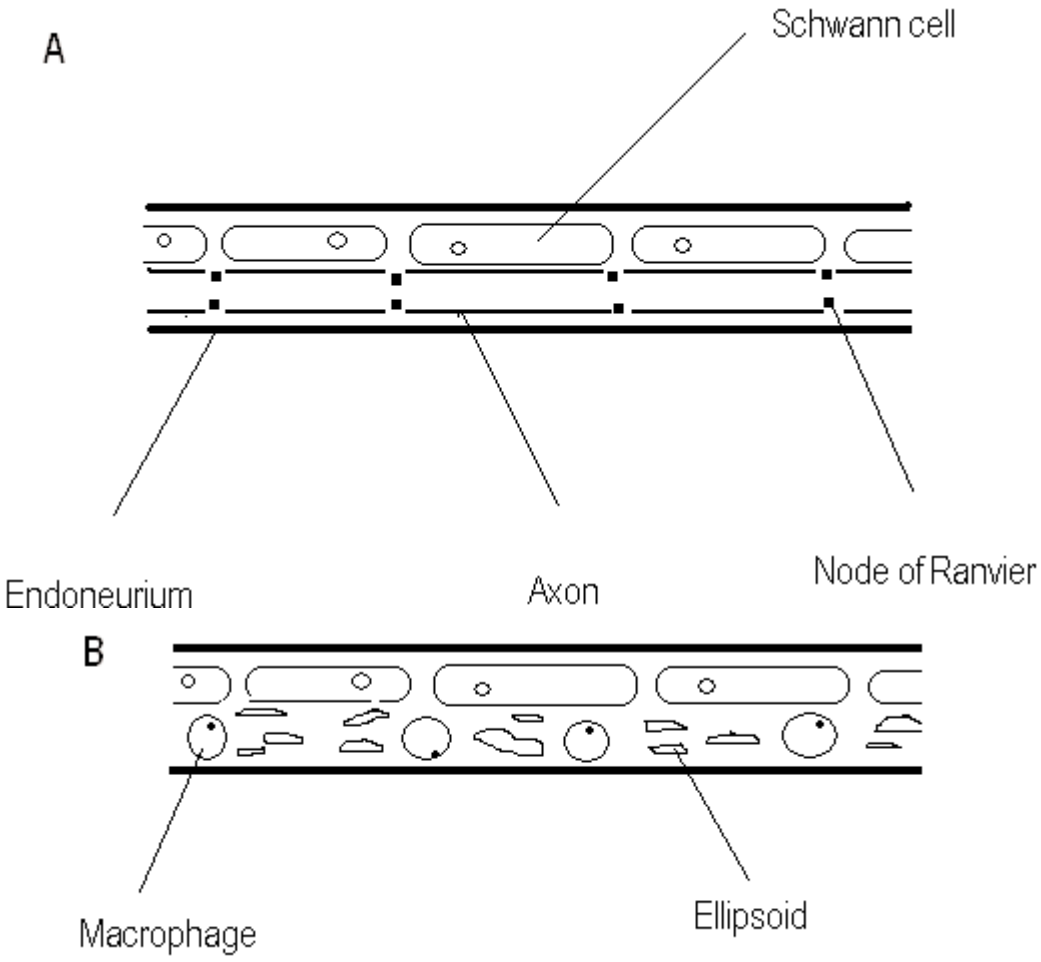

Figure 2. A normal uninjured nerve fibre. (A) Early events of Wallerian degeneration taking place in an injured nerve. (B) The axon has been degraded into ellipsoids and is being engulfed by macrophages.

Regeneration in the Proximal Segment

As with distal segment nerve degeneration, changes in the proximal segment also depend on the severity of injury. Proximal degradation is usually minimal. However, with more severe injury the cellular body may be damaged, in which case the entire proximal segment undergoes Wallerian degeneration. The cell body and axons are interdependent in recovery. A predictable phenomenon is that within 6 hours of injury, the nucleus migrates to the periphery of the cell where Nissl granules and rough endoplasmic reticulum break up and disperse. This phenomenon is called chromatolysis. It is thought to act as a signal for glial cells to extend processes to the affected neuron and interrupting synaptic connections, providing isolation of the affected neuron and thus permitting recovery. The situation is complicated in the proximal segment due to apoptosis. The incidence of apoptosis related cell death in dorsal root ganglia neurons ranges from 20-50%[8].

Regeneration of peripheral nerves

As discussed earlier, recovery is complete in 1st degree (neuropraxia) and 2nd degree injuries. With more severe damage, as per the degeneration phase, the process of regeneration is dependant upon the severity of injury and site of the lesion. In a mixed nerve there is no difference between growth and maturation of the sensory and motor fibres[9]. In less severe injuries, the regenerative and reparative processes begin almost immediately .With more severe injuries, however, regeneration begins only once Wallerian degeneration is complete. The sequence of regeneration is anatomically dependant, beginning at the cell body's proximal segment, proceeding to the distal segment, the injury site itself , and finishing at the end organ. Degradation provides the right environment for regeneration. Various genes are up-regulated primarily to produce vast amounts of lipid and protein for axonal regrowth[11]. The proximal stump branches, or growth cones, contain anchoring filopodia that extend towards the distal stump. Schwann cells in the distal stump extend to engage with the filopodia via cell surface adhesion molecules. It is not surprising that if the gap between these two stumps is wide, regeneration does not occur without surgical repair. Failure of the two stumps to meet produces a neuroma consisting of whorls of regenerating axons trapped in scar tissue at the site of the initial injury. Following amputation of a limb, an amputation neuroma can be a source of severe pain. The first signs of axonal re-growth take place between 24 hours and 1 week post injury. The peripheral nerve's ability to regenerate lasts approx. 12 months after injury [6]- an important factor in the timing of surgery.

Management of Peripheral Nerve injuries

As with any type of trauma A B C (Airway, Breathing, Circulation) should be assessed and maintained if appropriate. Trauma life support should be instigated if necessary. The grade of a nerve injury may be ascertained by interpreting clinical and neurophysiological findings according to Seddon's classification[4].

The level of the injury can usually be deduced by thorough examination and knowledge of the anatomical distribution of the nerves. Two-point discrimination is particularly useful for assessing sensation in the hand as it is an objective measurement and normality (approx. 4mm on the finger pulps) excludes significant nerve injury[10]. With neuropraxia supportive measures are all that is required. This is usually also the case for milder cases of axonotmesis. With more severe forms of axonotmesis, surgery may be required. A proper assessment of the degree of damage may necessitate exploration under anaesthesia. Assessing compound muscle action potential with electro-diagnosis is also helpful to classify the injury (although initially axonotmesis and neurotmesis pictures appear identical

Table 1. Adaptation of Seddon's Classification of Nerve Injury4

	Neuropraxia	Axonotmesis	Neurotmesis
Motor loss	Complete	Complete	Complete
Sensory loss	Partial sparing	Complete	Complete
Autonomic function	Spared	Absent	Absent
Nerve conduction distal to injury	Present	Absent	Absent
Fibrillation on EMG*	Absent	Present	Present
Recovery	Rapid, Complete	1mm per day, good	1mm per day, always incomplete

* electromyography

and only differ as time elapses)[11]. Neurotmesis can easily be detected upon exploratory surgery as the nerve can be seen to be completely transected. In neurotmesis, surgery is indicated as there is no hope of spontaneous recovery.

The timing of surgical nerve reconstruction is important for optimal recovery. In every case of acute injury, the surgeon must decide whether a primary repair or an early secondary repair is the treatment of choice. Timing can be divided into immediate, early (1 month), delayed (3-6 months), and late (1-2 years or more). Immediate repair is preferred when the nerve has been lacerated and there has been a clean cut. The nerve ends should also be uninjured. If there is a high degree of injury surrounding the nerve, surgery may have to be delayed until inflammatory processes operating in the vicinity have dampened.

Early reconstruction is preferred for injuries caused by blunt trauma or avulsion, which are thought to have caused complete nerve destruction. Nerve grafts are usually indicated as the nerve ends have usually contracted and/or scars need to be resected. Autologous nerve grafts provide regenerating axons with a natural guidance channel, populated with functioning Schwann cells surrounded by their basal lamina[12]. Harvesting of nerve grafts results in co-morbidity that includes scarring, loss of sensation, and possible formation of a painful neuroma. The graft used is usually from the sural nerve.

Delayed reconstruction is preferred when the degree of injury has not yet been ascertained. For example, if the extent of axonotmesis is unclear, then it is recommended to hold off on surgery, as natural recovery is better than surgical repair. However, the quality of motor recovery decreases steadily after a 6 month delay of repair[13]. Late reconstruction is generally only carried out for pain control, such as neuroma resection. The current surgical standard is epineural repair with nylon suture. To span gaps that primary repair cannot bridge without excessive

tension, nerve cable interfascicular autographs are employed[14]. It has been found that an injury to a peripheral nerve trunk associated with end-to-side nerve repair, activates neurons and non-neuronal cells (via nuclear translocation of activating transcription factor 3) and may contribute to sprouting of axons into the nerve attached end-to-side[15]. It is unclear how much this technique is being used clinically however.

Surgical success appears to vary widely. Sensory recovery appears to be similar for most nerves[16]. However, motor function varies according to individual nerves. In one study, the motor recovery in ulnar nerves was 71% lower than that in median nerves[17].
It appears that age (younger patients fare better), site, the nerve injured, and delay, significantly influence prognosis after micro-surgical repair. After surgery the affected area should be immobilised for approx. 6 weeks. After this, movement is encouraged and physiotherapy is most useful. Strength exercises may be performed along with the use of electro-stimulating devices. These are thought to improve synchronisation of motor unit firing and increase efficiency of motor units. After several weeks there is muscle fibre hypertrophy which results in a further increase in strength. Patients should be followed up regularly in the post-operative period to gauge extent of recovery. This should involve physical examination and electromyography (EMG).

The Future?

Current research is focussing on the development of a molecular therapy for nerve injury. Whether a novel therapy could be used exclusively on its own or used to augment surgery remains to be seen. Progress has been slow, as the testing of potential therapies is restricted to laboratory studies only. Neurotrophic factors which could theoretically expedite degeneration, and hence regeneration, have been the subject of intense study. It is thought that using natural factors in pharmacological doses could enhance recovery. One study found that the prognosis following nerve repair would be enhanced by the controlled release of a combination of neurotrophins, glial-cell-line derived neurotrophic factor family ligands (GLFs) and the neuropoietic cytokines (the three main families of neurotrophic factors) at higher concentrations than used in previous conduit designs[18]. Other studies appear to focus on the downstream effects of these neurotrophic factors; looking at for example the suggestion that up-regulation of HNK-1 glycan can promote functional recovery[19].
Despite a huge amount of studies, treatment for peripheral nerve injury remains largely unchanged.

CONCLUSION

It can be seen that peripheral nerve injury and repair is a highly sophisticated and active process. The effects of a nerve injury can be devastating. It is hoped that in the future, more successful treatments will become available. In the meantime, clinicians, physiotherapists, occupational therapists and the greater multidisciplinary team involved, will undoubtedly continue to provide expertise and outstanding care.

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Sleep and REM Behaviour Disorder: Much More than Sleep Walking

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Clinical Points

- REM sleep is characterised by saccadic eye movements, muscle atonia, and vivid dreams
- The key complaint in RBD is violent dream enacting behaviour during REM sleep which results in harm to the patient and their bed partner
- RBD is linked to neurodegenerative conditions especially Parkinson's disease and dementia, as well as narcolepsy
- RBD is a chronic disorder but highly treatable with clonazepam taken at night before sleeping
- RBD must be differentiated from nocturnal sezures, sleep walking, sleep terrors, obstructive sleep apnoea with agitated REM-related arousals, periodic limb movement disorders and malingering

ABSTRACT

Rapid eye movement (REM) sleep is characterised by the active neurological processes which underpin dreaming and result in the paralysis of all somatic musculature, except extra-ocular muscles and the diaphragm for continued respiration. Recently, a sleep parasomnia, termed REM Behaviour Disorder (RBD), has been described, in which patients physically act-out their dreams in an excited and sometimes violent manner. This paper presents two clinical vignettes describing patients with RBD and reviews the available literature on the subject.

CLINICAL VIGNETTES

Mr B, 67 year old male, presents electively to the neurology outpatient clinic following episodes of acting out during his dreams. These spells occur most nights around 3 a.m., when the patient is likely to be in REM sleep. He describes a typical dream where he is a child on a flight home from Alaska which stops over in Seattle. He misses his connection and a stranger offers to take him on a sightseeing tour of the city. When he gets into the stranger's car a gun is pointed at his head. In order to escape he jumps from the car, at which point, he physically jumps off his bed and dives to the floor, injuring his neck. On this particular occasion he also kicked his wife in the chest and, as a result, she now sleeps in a separate room.

Mr S, 23 year old male, reports having trouble with his sleep since childhood. His main complaint is that he sometimes has intense dreams which he re-enacts. Recently, he dreamt his wife was attempting to place a spider on his face, resulting in him assaulting her via a blow to the stomach. His wife is understandably distraught and feels he needs medical attention.

INTRODUCTION

Normal Sleep

Sleep is defined as a state of unconsciousness from which a person can be aroused with a stimulus and restored to a state of full responsiveness[1]. This definition serves to distinguish sleep from a coma where a person cannot be aroused to a state of full responsiveness, regardless of the intensity of the stimulus[1].

Sleep is an essential function of the brain and is organized to produce predictable electrophysiologic patterns that form the basis of behavioral sleep[2]. The neural centers involved in the production and regulation of sleep patterns are located in the brainstem, diencephalon, thalamus and also involve the cortex secondarily[2]. Sleep is also generated by the influence of hormones, neurotransmitters, and active peptides[2].

The sleep-wake cycle is coupled with the external alteration of light and dark. It follows a 24 hour pattern, or circadian rhythm, which is mediated by the suprachiasmatic nucleus of the hypothalamus[2]. It is linked to the retina via the retino-hypothalamic tract which conveys photic information in order to synchronize the circadian rhythms with the light-dark cycle[2].

Brain activity alternates between wakefulness and sleep[2]. Sleep is further divided into two distinct states, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. During the night, a person alternates between NREM and REM sleep. At the start of the night, the person experiences more NREM sleep which is the deep, restful slow wave sleep after being awake for many hours[2]. REM sleep occurs in episodes that occupy approximately 25% of the sleep time in young adults and normally tends to

recur every 90 minutes[2]. Each state has distinct anatomic, electrophysiologic, biochemical, and behavioral characteristics which allows them to be studied independently.

The electroencephalogram (EEG) is used to study the various stages of consciousness and sleep[2]. Electrodes are placed on the scalp but in some special cases they are inserted subdurally or even in the cerebral cortex to measure the electrical activity of the brain. The electrical activity reflects the electrical signals (postsynaptic potentials) from a large number of neurons[3]. Electrical currents are not directly measured but rather voltage differences from various parts of the brain are used. EEG is a useful method of studying brain activity since it is generally non-invasive and highly sensitive[3]. EEG can detect changes in electrical activity in the brain in a millisecond. It is a useful tool for studying patients with neurological conditions such as epilepsy, dementia, brain death and coma[3].

Wakefulness

The neuronal areas of the brain involved in promoting wakefulness are primarily found in the reticular formation[4]. These neurons constitute a system located in the reticular formation of the brainstem, thalamus, posterior hypothalamus, basal forebrain, and subthalamus[4]. The tonic activity in the reticular activating system is reinforced by sensory input via collaterals in order to maintain wakefulness[4]. Reticular system activation ascends via the brainstem reticular formation into the thalamic system from where it is transmitted to the cortex of the forebrain. There is also an alternative extrathalamic route which originates in the subthalamus, posterior hypothalamus, and basal forebrain that eventually projects to the entire cortex[4].

Table 1. *Stages of Non-REM Sleep*

Stage	EEG Findings	Distribution	Fact(s)
Stage 1	Disappearance of the alpha wave (8-12Hz) and appearance of theta wave (4-7Hz)	5%	
Stage 2	Sleep spindles (7-14Hz) and k complexes	45%	Longest stage of all the sleep stages.
Stage 3	Appearance of delta waves (<2Hz)	12%	Also called slow wave or delta sleep. Hardest to arouse. Tends to vanish in elderly.
Stage 4	Continuation of delta wave	13%	Same as for Stage 3
REM	Bursts of sawtooth waves	25%	Easiest to arouse. Lengthens in time as night progresses. Increased during second half of the night.

NREM Sleep

NREM sleep is characterized by slowing of the electroencephalograph (EEG) rhythms, high muscle tone, and absence of eye movements. There are four stages which are summarized in Table 1.

Sleep appears when the sleep promoting neurons become active and the wakefulness-maintaining mechanism fades[2]. Synchronized sleep is an expression of the unified activity of many different neural networks. EEG findings are summarized in Table 1 and serves to reflect the activity of these networks. Neurons involved in generating synchronized sleep are found in the anterior hypothalamus, preoptic area, solitary tract nucleus of medulla, raphe nuclei of the brainstem, reticular thalamic nuclei, basal forebrain, and orbitofrontal cortex[2].

Before synchronized sleep occurs, it is preceded by light transitional sleep[4]. Both the light transitional sleep and synchronized sleep form the NREM state. During the light transitional sleep, which occurs before Stage 1 of NREM, it is common for people to experience an involuntary muscle twitch known as a hypnic or hypnogagic jerk[4]. This is completely normal, especially when people are very tired or not sleeping comfortably. Stage 1 sleep is characterized by the disappearance of alpha waves (8-12Hz) which are characteristic of wakefulness, and appearance of theta waves(4-7Hz). This stage only lasts for a few minutes and may recur briefly during the night after body movements[4].

Stage 2 sleep appears five to seven minutes later[4]. Stage 2 sleep, which is the longest stage of sleep, is characterized by sleep spindles (7-14Hz). The functional significance of sleep spindles are unknown, but they are associated with the blockade of synaptic transmission of afferent impulses through the thalamus when there is a loss of consciousness. Spindle frequency potentials and spike discharges in the neocortical neurons are recorded on the EEG when there are bursts of activity in the thalamocortical networks[4]. K complexes are also seen randomly in this stage of sleep and are thought to occur in response to auditory stimuli. For example, when researchers knocked on the door when people were in stage 2 sleep, K complexes appeared, followed by sleep spindles.

Stage 3 sleep appears 15 to 30 minutes later and is known as slow wave sleep or delta sleep (due to delta waves (<2Hz) on EEG). Serotonergic neurons located in the raphe nucleus in the brainstem promote the emergence of slow wave sleep 4. In this stage of sleep it is hard to arouse an individual and it is also virtually nonexistent in the elderly[4]. Stage 4 is the maintenance of the delta waves on the EEG. Essentially, stages 3 and 4 sleep last 30 to 45 minutes and are followed by a reversal to stage 2 and the onset of the first REM episode[4]. This marks the end of the first sleep cycle.

REM Sleep

REM sleep is also known as paradoxical sleep or desynchronized sleep. It generally lasts 5 to 30 minutes and on average appears every 90 minutes[5]. When a person is over-tired, the bouts of REM sleep tend to be short and possibly even absent. REM sleep is considered paradoxical because the brain is quite active but the person is not fully aware of his or her surroundings. It is difficult to arouse patients from REM sleep with sensory stimuli, as opposed to deep slow wave sleep, yet people usually awaken spontaneously in the morning during an episode of REM sleep. Overall, the brain's metabolic activity is increased by as much as 20% and EEG shows that the pattern of brain waves is similar to those occurring during wakefulness[5]. The cortical EEG rhythms are desynchronized due to the activation of large nerve cells in the central midbrain reticular formation[5]. The latency to REM is shorter in sleep deprived subjects, neonates, patients with narcolepsy, and subjects withdrawing from alcohol and REM suppressant medications[5].

There are two main components in REM sleep: *tonic* and *phasic*. In the *tonic* phase, muscle activity is suppressed and the EEG shows low-voltage mixed frequency activity. Also, no phasic REM components are observed and the respiratory rate is regular[5]. In the *phasic* component of REM sleep the muscles twitch, rapid eye movements occur, and heart rate as well as respiratory rate become irregular. It is also characterized by the appearance of sawtooth waves, runs of 2-6Hz notched waves, which may be seen in the frontotemporal region, usually in association with bursts of eye movements[5].

REM sleep is generated by a set of unrelated phenomena produced by different areas of the pons and caudal midbrain[5]. Although it is not the unique area for the production of REM sleep, the nucleus reticularis pontis oralis is the region of the brain most critical for the production of REM sleep. This nucleus is located in the pons and provides input to the entorhinal cortex of the hippocampus to produce highly synchronized theta rhythms, which are present continuously during REM sleep[5]. This EEG finding resembles that of stage 1 sleep[5].

REM sleep stage is associated with active dreaming and extreme inhibition of muscle tone throughout the body, except in the diaphragmatic muscles and eye movement muscles[6]. The inhibition is mediated by cells in the peri-locus coeruleus area. These cells become active and stimulate the inhibitory nerve cells of the magnocellular reticular nucleus via the tegmento-reticular tract[6].

However, despite inhibition of the motoneuron activity during REM sleep occasionally brief clonic contractions of facial and distal extremity muscles do occur. This is part of the phasic component of REM sleep and is due to excitatory potentials reaching motoneurons at irregular intervals[6].

The rapid eye movements are saccadic, conjugate eye movements in the horizontal, vertical, and oblique planes. Ponto-geniculo-occiptal (PGO) spike generation is associated with generation of rapid eye movements both in the waking state and in REM sleep[7]. The PGO spike originates in the dorsolateral pontine tegmentum and projects to the lateral geniculate nucleus. Each half of the pons functions independently in the generation of PGO spikes and, therefore, each pathway for propagation can be interrupted independently[7]. PGO waves are speculated to eventually reach cortical areas and trigger fragmentary imagery that we consider dreams. PGO spikes can be triggered by cholinergic activation or inhibited by serotonin[7].

During REM sleep several physiologic changes occur. The heart rate is accelerated, blood pressure is variable, the respiratory rate increases due to the phasic (intermittent) activation of the medial and lateral parabrachial nuclei in the pons[5]. These nuclei appear to exert a modulatory effect over the bulbar neurons (cranial nerves of the lower brain stem). The respiratory fluctuations in REM sleep are controlled directly by the pneumotaxic centers of the brainstem and are independent of peripheral metabolic changes (oxygen saturation, pH of blood etc.)[5]. Other changes which have been observed include increased intracranial pressure, decreased cardiac output and urine flow, increased cerebral blood flow and sympathetic tone is losoely coupled with phasic changes in parasympathetic tone[5].

Dreaming

Dreams are the subject of much interest in neurology and psychiatry. While there has been some interesting research, it is hard to elucidate the exact nature of dreams. Dreaming can occur in any stage of sleep, but it is most common in REM sleep[7]. Dreams do occur in slow wave sleep, and sometimes night terrors as well, but they are not usually remembered[7]. Dreams in NREM are associated with somatic muscle activity (due to the high muscle tone) as opposed to REM sleep (due to muscle atonia)[7]. This is the stage where night terrors are experienced. Usually seen in young children (but can be seen in any age group), night terrors are characterized by the awakening from Stage 4 sleep with a strong sense of fear and panic[8]. It is often impossible to completely awaken the subject and eventually he or she settles back to sleep. However, when the subject is asked about the episode, he or she is more than likely not to be able to recall the event[8].

When subjects are awakened from REM sleep they report dreaming 85% of the time. EEG evidence shows high levels of PGO waves that originate in the pontine area travel to the lateral geniculate nuclei in the thalamus provideing excitation to the forebrain. Autoradiographic experiments during REM sleep have shown increases in glucose metabolism in the visual cortex which may be the input for the dream visual experiences[7]. Sensory system activation during the dreaming experience always involves

the visual system and auditory experiences appear in about 65% of dreams[7]. Less commonly, spatial experiences such as floating or flying occur but these are most likely associated with the vestibular system. Rarely experiences involving tactile, taste or smell perceptions occur. Pain is almost never incorporated in dreams[7].

Despite motor system excitation during dream mentation, motor commands are not executed
because of the powerful inhibition of motoneurons present in REM sleep[7]. Experimental evidence indicates that cortical and subcortical motor structures, which mediate complex organized movements, are activated during the dream state[7].

There are two main proposed theories regarding dreaming - the activation synthesis theory and continual activation theory. The activation theory, proposed in 1977 by J. Hobson, asserted that sensory experiences where due to PGO spikes[9]. Essentially PGO spikes originate in the pons and stimulate higher midbrain and cortical structures leading to rapid eye movements. This internally generated information is thought to lead to the synthesis of dreams[9]. It was assumed that the same structures producing REM sleep also led to the generation of sensory information. Since neurotransmitters such as norepinephrine and serotonin are present in decreased concentrations during REM sleep this leads to memory, attention and lack of orientation[9].

Later on, further research on dreaming was done on patients with various brain injuries by M. Solms[10]. He discovered, as he questioned patients about their dream experiences, that patients with parietal lobe damage stopped dreaming (this was also shown in Hobson's theory). Patients, however, with brain stem damage did not lose the dream experience, so this raised doubts that the brain stem was the source of dreams (this was contrary to Hobson's theory)[10]. Solms viewed dreaming as a complex function involving several brain structures and felt that REM sleep and dreaming were not directly related[10].

In 2001, a study showed that dreams may serve to help the brain consolidate memories by illogical locations, characters, and dream flow[11]. These conditions may occur in REM sleep because there is a decreased flow of information between the hippocampus and neocortex[11]. This lack of communication may be linked to increased levels of cortisol which generally occurs during REM sleep[12].

Neurotransmitters and Sleep

The key neurotransmitter systems involved in controlling the sleep-wake cycle are monoaminergic (noradrenaline, dopamine), cholinergic and histaminergic neurons[13]. Gamma-aminobutyric acid (GABA) neurons located in the anterior hypothalamus and basal forebrain play an important role in sleep control. While most neurons have a very minimal role in NREM sleep, GABAergic neurons are the most active during this state compared with REM sleep or the awake state. These neurons discharge at increasing rates during sleep and maintain high levels of GABA. The main function of GABAergic neurons is to inhibit cells involved in arousal in order to induce sleep. For example, the GABAergic neurons inhibit cholinergic neurons in the basal forebrain[13]. These cholinergic neurons are one of the key forebrain arousal systems of the brain, so when they are inhibited the cortical activity diminishes. However, cholinergic neurons are active during the REM state and are involved in generating PGO spikes which are linked to dreaming[13].

Histaminergic neurons, found in the posterior hypothalamus, play an important role in arousal and maintaining wakefulness[13]. Lesions in this area produce a comatose-like continuous sleep. These neurons are inhibited by GABAergic neurons during sleep in order to inhibit the awake state. Histaminergic neurons are virtually inactive during REM sleep. It is interesting to note that antihistamine medications which cross the blood brain barrier make patients drowsy[13].

Norepinephrine, which is found in the locus ceruleus of the pons, is also inactive during REM sleep[13]. This neurotransmitter along with serotonin plays a role in maintaining muscle tone and motor activity during the wakeful state. Serotonergic neurons are located in the raphe nuclei which extends in the midline from the midbrain to the medulla. These neurons are also inhibited by GABAergic neurons during sleep[13]. They may play an important role in regulating the phasic events of REM sleep in that if the serotonergic neurons are destroyed, the inhibition on the phasic events would be released. Essentially, when GABA is applied to adrenergic and serotonergic neurons, REM sleep is triggered[13].

Another substance that plays a role in sleep is adenosine[13]. The adenosine neurons are found in the hypothalamus and the receptors are blocked by caffeine and xanthines. CSF (cerebrospinal fluid) borne factors and opiate peptides, such as enkphalin, b-endorphin, and dynorphins, could play an important role in initiating and maintaining sleep[13]. These neuromodulators are crucial for sensory modulation and analgesia[13]. Several blood borne factors, such as insulin and cholecystokinin, which are released from the gut after meals, tend to promote sleep[13].

Recently, another peptide and its variants, hypocretin I and II (also named oxrexin A and B) were discovered in the posterior and lateral hypothalamus[13]. Hypocretin has an unusual relationship with amino acid neurotransmitters such glutamate and GABA[13]. In the locus cerelus, hypocretin was shown to release both glutamate and GABA producing an excitation and inhibition which may

stabilize the electrical polarization of the membranes[13]. Absence of hypocretin is considered as the basis of the behavioral and physiologic instability which occurs in narcolepsy[13].

REM Sleep Behavior Disorder

Definition

The key feature characterizing REM Behavior disorder (RBD) is the loss of muscle paralysis during otherwise intact REM sleep[1]. REM sleep is the stage of sleep wherethe most vivid dreaming occurs and patients with RBD have a tendency to act out their dreams[1]. This behaviour can be violent in nature and distressing to the patient, as well as their bed partner. Despite the complex pathophysiology behind RBD, it is an easy illness to diagnose and treat appropriately[14].

Animal Model

The defining features of REM sleep are rapid eye movements, desynchronized EEG, and muscle atonia. The key clinical feature of RBD is loss of REM atonia with behavioral relase during REM sleep. This leads to serious clinical risk of sleep related injuries because dreams crash into reality.

When bilateral dorsolateral pontine tegmental lesions in cats were introduced, the REM atonia was lost permanently[15]. This was the only lesion in the brainstem which produced such effects. These cats always displayed hallucinatory behaviors during unequivocal REM sleep which resembled dream enactment[15]. The behaviors were always stereotypic and repetitive without any external influence or provocation. It was almost always an attack behavior that was displayed, but sexual and feeding behaviors were never observed in these cats[15]. Also, these cats were never inappropriately aggressive during wakefulness[15]. This model most closely resembles the findings seen in human RBD.

Researchers identified four levels of dream-enactment behavior in the cat model of RBD[15]. The level of the behavior depended on the location and size of the pontine tegmental lesion. The levels are shown in Table 2.

Table 2. *Dream-Enactment Behavior as seen in Cats*

Level of behavior	Behaviors experienced by cats
1	Minimal syndrome with limb or trunk jerking. Intermittent violent behavior.
2	Exploratory behaviors – head raising and turning, grasping, searching
3	Stalking imaginary prey. Episodic attack behavior
4	Locomotion

Brain mechanisms originating in the peri-locus ceruleus alpha nucleus of the pons are responsible for the REM atonia[6]. Neurons from this region have excitatory projections to the nucleus reticularis magnocellularis in the medulla. These neurons in the medulla have an inhibitory descending projection, more powerful than the competing excitatory projections, to the spinal alpha motoneurons. This produces the hyperpolarization and muscle atonia leading to REM-atonia[6].

However, these animal experiments reveal that the loss of atonia during REM sleep is not sufficient in itself to generate RBD[15]. In fact, it is interesting to note that unlike the animal model, the pons are rarely involved in the pathogenesis of RBD in humans, as shown with extensive neuroanatomical and neurophysiologic testing[15]. It is not completely certain which area of the brain is linked to the pathogenesis of RBD in humans. The manifestations are still similar in both humans and cats.

Aetiology and Epidemiology

Although the disorder was identified as earlier 1966, RBD was not formally recognized and classified until 1986-87 by the International Classification of Sleep Disorders. RBD can be either an acute or chronic disorder. The acute form is generally seen during withdrawal from ethanol or sedative-hypnotic abuse, as well as anticholinergic medications[16]. REM behavior disorder can also be drug-induced by tricyclic antidepressants, MAOIs and SSRIs[16]. It is difficult to study the acute form of REM behavior disorder since it is transient and often associated with the symptoms of withdrawal[16].

The chronic form is most often presented to physicians for evaluation. Generally, the disorder affects older individuals (over age 50) and has a male predominance (80%)[17]. Approximately a quarter of the patients have a prodromal phase, which is often lengthy and involves subclinical behavioral release during sleep. Some patients report a history of childhood sleepwalking or sleep terrors[18]. The chronic form is associated with other neurodegenerative conditions such as Parkinson's disease and related disorders, such as Lewy body disease. There is also a link between RBD and narcolepsy as well as cerebrovascular disease [19,20].

The neurologic disorder may precede or follow the appearance of REM behavior disorder. Extensive neurological investigations are only required if patient has a history or clinical exam suggestive of CNS pathology[19]. In several studies, it is shown that REM behavior disorder is possibly the first manifestation of parkinsonian disorder, which is otherwise considered in many cases idiopathic[19]. In one case series report, 38% of patients further went on to develop parkinsonism with 3.7 years of diagnosis and 12.7 years after initial onset of REM behavior disorder symptoms[17]. There is also an association with narcolepsy and when patients are treated with TCAs or SSRIs it may

induce or aggravate the REM behavior disorder20.

Clinical Features

The key complaint in RBD is that of violent dream-enacting behaviors that are potentially harmful to the patient, as well as their bed partner. Bed partners report that the patients generally have recurrent dream enacting behaviour ranging from laughing, talking, yelling, gesturing, grabbing, punching, kicking, crawling, and jumping out of bed. Generally, the dream enacting behaviors do not begin until 2 hours after sleep onset which generally coincides with typical REM onset (sleep cycles last 90 minutes and end with REM sleep)[17]. However, most of the time these dream enacting behaviors occur in the early morning hours when REM sleep predominates[17]. The frequency of these RBD episodes range from several episodes nightly, to one episode every 2-3 weeks[17].

These behaviors occur within REM sleep but are not accompanied by tachycardia and do not occur during arousal from REM sleep. Complex behaviors are generally aggressive and exploratory, but never appetitive (feeding, sexual)[17]. It is important to note that patients do not reenact customary dreams but distinctly altered dreams usually involving violence and aggression.

Unless the RBD is linked to narcolepsy, daytime multiple sleep latency testing rarely documents objective daytime sleepiness[20]. The explanation for this phenomenon is obscure, but one clue provided in research is RBD patients appear to have a higher percentage of restful slow wave sleep. This may be a compensatory mechanism in the body after tremendous energy expenditure in agitated REM sleep[20]. Patients with RBD generally spend 75% of their time in slow-wave sleep[20].

Diagnosis

The diagnosis of RBD is made clinically, based on the history elicited from the patient and usually their bed partner. There are several important questions a physician should ask during the history about their sleep behaviours[14]. Patients should be asked about limb or trunk movement during sleep and if it is linked to them trying to enact their dreams. It should also be noted if the patient injured themselves or their bed partner during sleep and if they ever fell out of bed during sleep[14]. Also, patients should be asked if they were ever talking loudly or screaming during sleep[14].

Disruptive nocturnal behaviors should be extensively evaluated by the physician. Generally, this involves asking the patient about their sleep habits, medical and psychiatric history, and evaluating their alcohol and substance use. Patients should also undergo neurologic testing since there is a high association with RBD and parkinsonism and dementia[14]. If history and neurologic examination appears positive, an MRI scan may be indicated. It is important for the physician to rule out EEG epileptiform activity during sleep[14]. Patients should be monitored continuously with videotaping overnight during polysomnography (PSG)[14].

PSG is a multi-parametric test carried out to study sleep. It consists of monitoring the patients ECG, pulse oximetry, EEG, nasal and oral airflow, electrooculogram (EOG) and electromyography (EMG)[3]. EOG is used to monitor eye activity which aids in the determination of when REM sleep is occurring. Two electrodes are placed slightly out and above the outer canthus of the right eye and slightly out and below the outer canthus of the left eye. The electrodes determine the activity of the eye using the electropotential difference between the cornea and the retina (cornea has a positive charge in relation to the retina)[3]. EMG studies are used to measure muscle tension in the body and monitor excessive amount of leg movements during sleep[3]. Four leads are positioned on the body. Two leads are placed on the chin, with one above the jaw line and one below it. The other two leads are placed on the anterior tibialis of each leg to monitor leg movements. The PSG gives the physician an extensive clinical picture of what is occurring during the time the patient is asleep[14].

Differential Diagnosis

RBD is one of several disorders that manifest with violent behaviors during sleep. Things to consider in patients presenting with this clinical history are nocturnal sezures, sleep walking, sleep terrors, obstructive sleep apnoea with agitated REM-related arousals, periodic limb movement disorders and malingering[21].

The history of dream enacting behaviour does not automatically confirm the diagnosis of RBD. This behavior can appear in sleepwalking and sleep terrors[21]. In these disorders, vivid dream-like meditation can occur with precipitous arousals from slow wave sleep. Also, in nocturnal complex seizures, patients can have a peculiar dream-like aura, seizure-equivalent, or postictal experience[21]. Obstructive sleep apnoea is the most severe during the REM stage of sleep and often apnoea related arousals from REM sleep can be associated with persistent dreaming and agitated behaviors[21]. When periodic limb movement disorder persists in REM sleep, agitated dream related arousals can result in post arousal dream enactment. Nocturnal psychogenic dissociative episodes involve dream mentation related to dissociated memories of past physical and/or sexual abuse[21].

Treatment

Clonazepam is highly effective in the treatment of REM behavior disorder, in that it controls both the behavioral and dream-disordered components[22]. Patients typical respond immediately to a dose between 0.5-1.0 mg at bedtime and generally relapse when they fail to take

clonazepam on a given night[22]. The long term use of chronic, nightly clonazepam in treatment of RBD and other parasomnias has been documented in terms of efficacy and safety[22].

It is noted, however, that benzodiazepines may actually worsen sleep since patients can awaken more often during the night even though it is commonly prescribed for insomnia[22]. Also, another important side effect to be monitored, especially in the elderly, is dizziness which may lead to fainting and falls[22]. Physicians should monitor patients with RBD for side effects on a long term basis [22].

If the patient cannot tolerate clonazepam, there are several alternative therapies for RBD such as imipramine, clonidine, melatonin, gabapentin, and L-tryptophan[16]. Patients are treated for life for REM behavior disorder since it is a chronic problem where, if patients discontinue their medication, the symptoms will reappear[16].

CONCLUSION

It is important for physicians to recognize RBD for several key reasons. RBD is commonly associated with neurological disorders and, in fact, may possibly be the first sign of a disorder. RBD onset can precede the classical signs and symptoms of the neurological disorder by several years. This is commonly seen in Parkinson's disease patients. RBD may be induced or aggravated by various medications such as SSRIs, TCAs, MAOIs, and alcohol / drug withdrawal or abuse.

Also, RBD is easy to misdiagnose unless physicians are informed about the disorder. It may be considered psychiatric in nature since the common complaint is disturbed dreaming with violent behaviors enacting them. It may also be treated as nocturnal seizures or obstructive sleep apnoea. It is important that RBD is diagnosed and treated since it can potentially cause severe harm and injury to the patient and their bed partner.

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Statins: A review of benefits and risks

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4th Year Medicine

Clinical Points

- Statins have cholesterol and non-cholesterol (pleiotropic) effects
- Statins are central in the prevention of cardiovascular events associated with increased blood lipids and atherosclerotic lesions
- Recent and ongoing trials are investigating the benefits of early and intensive statin therapy versus current regimens, with promising results so far
- Cerivastatin was withdrawn in 2001 due to increased risk of rhabdomyolysis. Currently marketed statins have a superior safety profile, with the incidence of serious toxicities being extremely rare
- For at-risk patients, morbidity and mortality from cardiovascular events are greatly reduced with long-term statin use

INTRODUCTION

Since the groundbreaking Scandanavian Simvastatin Survival Study (4S) trial over a decade ago, the HMG-CoA reductase inhibitors, or Statins, have been central in the prevention of cardiovascular events associated with increased blood lipids and atherosclerotic lesions[1]. With coronary heart disease being the number one cause of death in the US[2], statins are proven lifesaving medications. Most clinical trials of statins report a significant reduction in relative risk of coronary events versus placebo. Of note, three of the secondary-prevention, landmark, statin trials have reported a reduction in the relative risk for all-cause mortality: a 30% reduction in the Scandanavian Simvastatin Survival Study (4S)[1]; a 22% reduction in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)[3]; and, a 13% reduction in the Heart Protection Study (HPS)[4].

Concerns regarding the safety of the HMG-CoA reductase inhibitors peaked after the voluntary, worldwide withdrawal of cerivastatin (Baycol®, Lipobay®) in August 2001, due to a markedly increased rate of fatal rhabdomyolysis -nearly 80 times greater than that for other statins available at the time[5]. In 2006, the National Lipid Association of America (NLA) appointed a Statin Safety Task Force to address these issues and evaluate statin safety. The NLA recently published its evaluation, finding statins to be generally well tolerated, having a high safety profile, with rare though potentially fatal side effects[6].

This review article will focus on factors relating to lipids, inflammation and statin therapy, with an emphasis on the benefits and risks of this line of treatment. To put these in context, both the risk of drug side effects and benefits for cardiovascular disease are expressed in events per person years of statin treatment. It is important to keep in mind that atherogenesis is a multifactorial disease process, thus therapy should be directed toward all the modifiable risk factors.

BENEFITS

Effects on LDL, Endothelium and C-reactive Protein (CRP):

Statins are structural analogues of 3-hydroxy-3-methylglutaryl-coenzyme A, and competitively inhibit the HMG-CoA reductase enzyme responsible for the first commited step in sterol biosynthesis. By reducing intracellular levels of cholesterol, the expression of LDL receptors in liver cells is up-regulated, leading to increased clearance of LDL from the bloodstream. Thus, their main effect lies in the reduction of LDL cholesterol[7].

Figure 1. Schematic representation of Statin effect on Cholesterol synthesis.

Statins also have numerous other effects, unrelated to lowering LDL, which are termed "pleiotropic" and include decreasing oxidative stress and vascular inflammation[8] while increasing the stability of atherosclerotic lesions[9]. Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction, which is characterized by damage due to reactive oxygen species which promote the release of transcription factors, growth factors, pro-inflammatory cytokines, chemokines and adhesion molecules[10]. In patients with coronary artery disease and hyperlipidaemia, statins improve endothelial function, decrease the plasma concentrations of tumor necrosis factor-α (TNF-α), and reduce morbidity and mortality[11]. Other cholesterol-independent effects of statins include the inhibition of platelet function by decreasing the production of thromboxane A_2 and decreasing the cholesterol content of platelet membranes, thus lowering their thrombogenic potential[12].

Statins are also known to reduce C-reactive protein (CRP) levels and a variety of experimental observations suggest a direct role for CRP in the pathogenesis of atherosclerosis. Specifically, CRP renders oxidized LDL more susceptible to uptake by macrophages, induces the expression of vascular-cell adhesion molecules, stimulates the production of tissue factor, and impairs the production of nitric oxide[13,14,15]. Ridker and Cannon concluded that patients with a low CRP level, after statin treatment, had better clinical outcomes than those with higher levels, regardless of the resultant level of LDL-cholesterol[16].

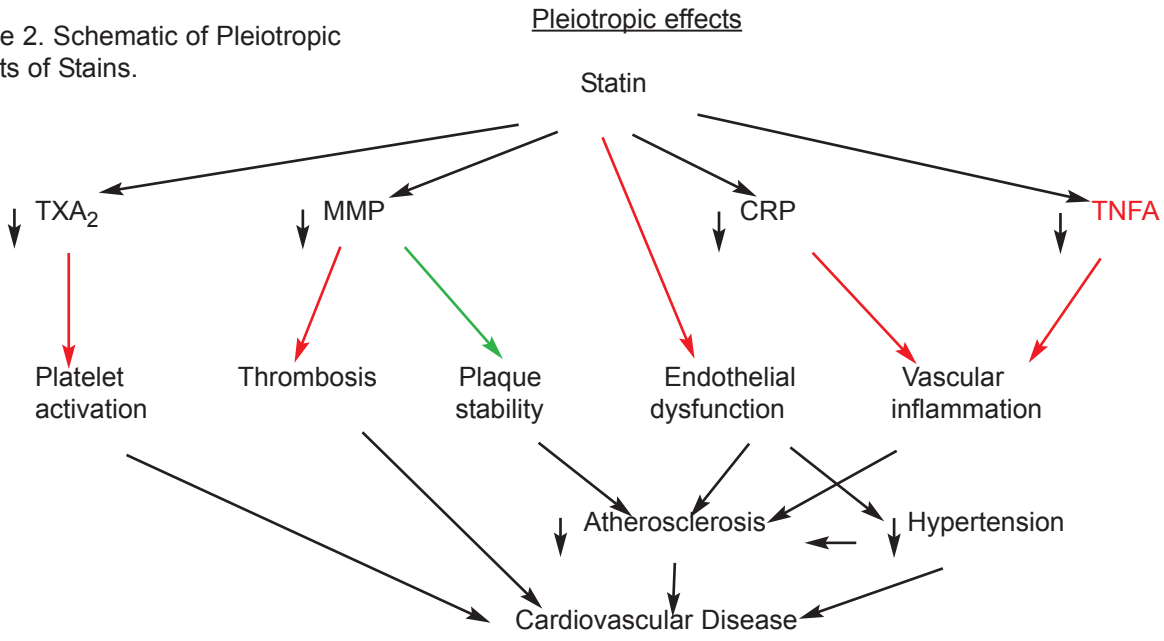
Clinical Benefits

Recent trials have demonstrated better clinical outcomes with intensive rather than moderate statin treatment. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial[17] demonstrated improved outcomes, with hospitalisation rates for heart failure significantly reduced after an acute coronary syndrome (1.6% with intensive therapy vs. 3.1% with moderate treatment). The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial[18] demonstrated reduced rates of progression of atherosclerosis after intensive (80mg atorvastatin) treatment when compared with moderate (40mg pravastatin) treatment.

Vigorous statin therapy can lead to a reduction in acute coronary events within 2-6 months. This is thought to be due to the mitigation of the inflammatory activity of macrophages, not the reduction in cholesterol. Intensive statin treatment produces greater reductions in both LDL-C and inflammatory markers such as CRP and interleukin-6 (IL-6), suggesting a relationship between these markers and disease progression[19]. Whether this anti-inflammatory action of statins is a direct effect, or mediated through reduction of LDL-C, is not yet fully understood but studies have shown that on sudden cessation of statins, CRP levels respond independent of LDL levels[20].

Vigorous therapy can also cause slow, minimal regression of plaques[21,22] and one study has reported a 6.3% reduction in atheroma thickness at 12 months[23]. Furthermore, stabilisation of atherosclerotic plaques occurs via the inhibition of matrix metalloproteinases (MMPs) release by activated macrophages within the lesion. This prevents the breakdown of the collagen in the fibrous cap, reducing the risk of plaque rupture, thrombosis, and the development of acute coronary syndrome[12].

Figure 2. Schematic of Pleiotropic Effects of Stains.



RISKS

Adverse Effects

Statins are responsible for a wide range of adverse effects, ranging from mild gastro-intestinal disturbances to life-threatening conditions such as rhabdomyolysis. When considering the risk-benefit profile of statin therapy, it is best to discuss side effects in terms of events per person year of treatment, as described by the NLA. Based on the data available, excluding Cerivastatin, current statins on the market have a very good safety profile and a proven reduction in mortality due to cardiovascular disease[24]. What follows is a summary of the major adverse effects reported.

Effects on Muscle

Among the most reported adverse effects of statins are nausea, diarrhea, constipation, and those relating to myotoxicity, ranging from mild myalgia to the rare instance of rhabdomyolysis. Clinical signs of rhabdomyolysis include severe muscle pain and tenderness on palpation, muscle weakness, and dark colored urine due to myoglobinuria. Rhabdomyolysis is associated with profoundly elevated creatinine kinase levels and acute renal failure secondary to myoglobinuria. Fatal rhabdomyolysis is the only substantial, well-defined cause of mortality associated with statin therapy. The estimated risk of developing rhabdomyolysis is 0.3 per 100,000 person years, with a fatality rate of 9%[25]. Combining any statin with a fibrate increases the risks for rhabdomyolysis to almost 6.0 per 100,000 person years[26]. On the other hand, survival benefit has a rate of 360 per 100,000 person years due solely to reduction in cardiovascular mortality[27].

The incidence of myotoxicity increases with the dose and concentration of statins, although the specific mechanism is unknown[28]. This finding highlights the importance of CYP450 drug interactions. Lovastatin, simvastatin and atorvastatin are metabolised by the CYP3A4 isozyme while rosuvastatin and fluvastatin are metabolised by CYP2C9. Thus, it follows that drugs which inhibit these enzymes (eg. verapamil, azole antifungals, macrolides, diltiazem and grapefruit juice) serve to decrease the metabolism of their substrates, leading to an increased risk of toxicity. Pravastatin pharmacokinetics, on the other hand, tends not to be influenced by administration of CYP inhibitors as it is not subject to CYP metabolism[29,30].

Effects on the Liver

Elevations in liver enzymes, specifically AST and ALT, to greater than three times the upper normal limit, are a dose-related effect of statins occurring in less than 1% of patients receiving initial treatment, and in 1-3% of those on higher doses (eg. 80mg atorvastatin)[31]. This effect is typically asymptomatic and transient, resolving spontaneously in the majority of cases even with continued therapy[32]. Furthermore, the epidemiological data on liver dysfunction and acute liver failure do not establish causality. The rate at which liver failure occurs in statin-treated patients is estimated at 0.5 -1 per 100,000 person years of treatment, which is equal to the background rate of liver failure in the general population[33]. This suggests either no relationship between statin therapy and liver failure, or that idiosyncratic reactions occur in some patients.

Current prescribing recommendations suggest liver function tests (LFTs) be performed at baseline and at 6-12 weeks after initiation of treatment, or when an increased dose is commenced. There is no evidence to suggest routine monitoring of LFTs in patients receiving statins, nor is it suggested that patients withdraw from therapy for an isolated transaminase level of 1-3 times the upper limit of normal (ULN), instead the test should be repeated and other aetiologies ruled out[31]. Patients should be warned of symptoms indicative of hepatotoxity, such as jaundice, malaise and fatigue.

Effects on the Kidney

Current literature provides no evidence that statins cause acute or chronic renal damage. Of note, the NLA statin safety task force found that "in the absence of infrequent rhrabdomyolysis, there is no evidence that the HMG Co-A reductase inhibitors cause renal failure or insufficiency"[34]. Results from the Prospective Pravastatin Pooling Project[35], which included results from 3 randomised clinical trials of pravastatin [1-Cholesterol and Recurent Events (CARE)[36], 2-LIPID Trial 3, and 3-West of Scotland Coronary Prevention Study (WOSCOPS)[37]] found that renal disease and failure occurred more frequently in placebo controls than in pravastatin-treated patients, with rates of 0.8% and 0.5% respectively. In addition, several studies suggest a potential protective effect of long-term statin treatment. A 2001 meta-analysis, involving 13 trials which studied the renal effects of lipid lowering medications, including statins, concluded that treated patients had decreased proteinuria and a lower rate of decline in glomerular filtration rate compared with controls[38]. As with hepatic function, current practice is to obtain a baseline assessment of renal function.

Effects on the Nervous System

Statins are highly lipophilic and thus have greater potential to cross the blood-brain barrier and affect the central nervous system. However, the balance between diffusion in and out of the CNS by transporters determines the actual exposure of the brain to statins. No effects of the lipophilic properties of statins have been shown with regards to efficacy and safety[39]. Law and Rudnicka estimate peripheral neuropathy caused by statins to have an incidence of 12 per 100,000 person

years[25]. Conversely, neurological data suggest that statins may have a beneficial effect on CNS disorders, including Alzheimer's disease and other dementias[40]. The NLA has determined the risk of peripheral neuropathy to be very small and recommends that if peripheral neuropathy develops, other aetiologies should first be ruled out. If no other cause is found, the statin should be withheld for 1-3 months. If, on cessation of treatment, symptoms improve, a presumptive diagnosis of statin-attributable neuropathy can be made. However, it is recommended that another statin and dose be considered because of the known benefits of therapy[6].

CONCLUSION:

Concerns over the safety of statins have increased since the voluntary withdrawal of Cervistatin from the world market, in 2001. Statins have been linked to adverse effects involving the liver, kidney, and nervous system. Nevertheless, it is important to note that in the absence of rhabdomyolysis, statins do not cause renal insuffiency. Baseline levels of liver transaminases and renal function tests are recommended before initiating treatment. It is also appropriate to measure transaminase levels periodically. Elevated LFTs represent a dose-related effect which may resolve spontaneously or with dose/drug change. Serious muscle toxicities with statins are extremely rare and given the magnitude of cardiovascular events avoided due to long-term statin therapy the benefits of these drugs most certainly outweigh the risks. As with all medications, patients and physicians should be aware of potential adverse effects and are encouraged to report all events.

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Sudden Cardiac Death in Athletes

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Clinical Points

- SCD in athletes is rare but significant as it can result in the unexpected death of a young, apparently healthy person
- The trigger for SCD is exercise in the presence of certain cardiovascular diseases, which can lead to fatal arrhythmias of the heart during physical exertion
- The most common causes for SCD in a young person:
  a. Hypertrophic cardiomyopathy
  b. Commotio cordis - unusual cause, but still second most common (especially in children due to their fragile thoracic skeletons)
  c. Congenital abnormalities of the coronary arteries
- Atherosclerotic coronary artery disease is the most common cause of SCD in athletes over 35. The incidence is 10-20 times more than in a younger person
- A selective screening strategy for SCD is the most favoured approach. Identifying those at risk via history and physical exam before undergoing further investigations is crucial

ABSTRACT

With the death of several well known athletes in the last thirty years, sudden cardiac death (SCD) has become of interest among many physicians. A series of studies conducted by American cardiologist and researcher, Dr. Barry J. Maron, have identified the major aetiologies in young athletes. In Ireland, Dr. Fionnuala Quigley, GP and lecturer in sports medicine, conducted a study that identified the main causes of SCD occurring in sport from 1987 to 1997. This data emphasized the causees of SCD in athletes over 35. This paper gives an overview of the main conditions that can lead to SCD in athletes, and discusses the methods and challenges of implementing a screening program.

INTRODUCTION

In 490 B.C., the Persian army attacked Greece in the Battle of Marathon. Despite being outnumbered three to one, the Greek army managed to encircle the Persians and emerge victorious. According to legend, a long-distance messenger, known as Phidippides ran 26 miles from Marathon to Athens, delivering the news of the Greek triumph. Upon delivering his message he dropped to the ground and died[1]. This story not only gave rise to an Olympic running event known today as the marathon but it was also the first recorded incidence of SCD in an athlete[2]. There have been very few documented cases of SCD occurring in sports since.

At the end of the twentieth century, the unexpected death of several high profile athletes led to an increased awareness of SCD. In 1986, 32 year old U.S. Olympic volleyball player Flo Hyman died on the sidelines after being substituted out during a game in Japan. In 1990, 23 year old U.S. college basketball player, Hank Gathers, collapsed on the court and died[3]. In 1994, 28 year old Russian Olympic figure skater Sergei Grinkov had a massive heart attack and died while practicing for an upcoming performance[4]. In 1999, 25 year old Gaelic footballer, Gerald Gallagher died of a heart attack during a match [5]. More recently, in 2004, 18 year old John McCall from Northern Ireland suddenly collapsed and died during a rugby match against New Zealand.

Aetiology in Younger Athletes

A 2003 study by Maron[6] compiled several causes for SCD in 387 American athletes aged 12-35 (Table 1). Male athletes were found to be three times more affected than female athletes, with the frequency of SCD increasing with age. The trigger for cardiac arrest was noted to be participation in sport in the presence of cardiovascular diseases, which can lead to fatal ventricular arrhythmias during physical exertion. Thus, most athletes who died suddenly were found to have cardiomyopathies, congenital coronary abnormalities, or atherosclerotic coronary artery disease (Table 1).

Hypertrophic cardiomyopathy is the most common cause of SCD in young athletes[6]. Half of those affected will describe symptoms of chest pain, dizziness, fainting, and abnormal breathlessness, particularly with exercise. Others may be asymptomatic, with SCD being the first sign of disease. Twenty percent of cases of hypertrophic cardiomyopathy are inherited, with the disease being passed on in an autosomal dominant fashion[2].

Table 1 - *Adapted from B.J. Maron. Sudden death in young athletes. N Engl J Med. 2003 (6)*

Cardiovascular Abnormality	%of Cases
Hypertrophic cardiomyopathy	26.4
Commotio cordis	19.9
Coronary artery anomalies	13.7
Left ventricular hypertrophy of indeterminate causation	7.5
Myocarditis	5.2
Ruptured aortic aneurysm (Marfan syndrome)	3.1
Arrhythmogenic right ventricular cardiomyopathy	2.8
Tunneled (bridged) coronary artery	2.8
Aortic valve stenosis	2.6
Atherosclerotic coronary artery disease	2.6
Dilated cardiomyopathy	2.3
Myxomatous mitral valve degeneration	2.3
Asthma (or other pulmonary condition)	2.1
Heat stroke	1.6
Drugabuse	1.0
Other cardiovascular cause	1.0
Long QT syndrome	0.8
Cardiac sarcoidosis	0.8
Trauma causing structural cardiac injury	0.8
Ruptured cerebral artery	0.8

Presentation is usually during the second decade of life and is characterized by dramatic ventricular thickening which particularly involves the ventricular septum. This excessive thickening of the heart muscle can lead to ventricular fibrillation, and death.

Commotio cordis, literally meaning “concussion of the heart,” involves a blunt, non-penetrating impact to the precordial region of the chest[7]. The kinetic energy of the impact is transmitted to the heart muscle and causes a fatal ventricular arrhythmia. For the impact to be fatal, it is thought that it must occur during the vulnerable phase of the cardiac cycle when the heart is relaxed. Commotio cordis is an unusual cause of SCD, but still ranks as the second most common aetiology[6]. Sports such as rugby, football, baseball, or martial arts, which may involve such trauma to the chest, are associated with an increased risk of commotio cordis[8]. Children are especially vulnerable due to their fragile thoracic skeletons. Pre-existing structural or electrical abnormalities of the heart have been speculated to render the individual more susceptible, yet there is no hard evidence to support this theory.

Congenital coronary artery abnormality is another common cause of sudden death in young athletes[6]. Such anomalies include the abnormal origin of the coronary arteries from the aorta, incomplete development of the arteries, coronary arteries buried deep within the heart muscle, and an abnormal origin of the left coronary artery from the pulmonary artery instead of the aorta[9]. The specific mechanism underlying death in these conditions is assumed to be insufficient blood flow to the heart during increased physical activity.

Aetiology in Older Athletes

A retrospective study was conducted by Quigley in 2000, which covered a 10 year period from 1987 to 1997, to observe the incidence of SCD associated with sports in the Republic of Ireland (Table 2)[10]. Fifty-one cases of SCD were reported by coroners. Ages of the individuals ranged from 15 to 80 years with a median age of 48 years. Males represented 50 of the cases. The cause of SCD in 42 cases was atherosclerotic coronary artery disease. Thirty-nine of these deaths occurred in men over the age of 35. Of interest, SCD in young athletes was rare, with only one case of hypertrophic cardiomyopathy; one case of a coronary artery abnormality; and no cases of commotio cordis.

Table 2 - *Adapted from Quigley F. A survey of the causes of sudden death in sport in the Republic of Ireland. The Brit J of Sports Medicine. 2000 (10)*

Type of sport associated with SCD	# of Sudden Deaths
Golf	16
Gaelic football	11
Jogging	5
Tennis	5
Marathon	2
Soccer	2
Swimming	2
Badminton	1
Table tennis	1
Squash	1
Rugby	1
Bowls	1
Horseriding	1
10 km Run	1
Pitch and putt	1

Atherosclerotic coronary artery disease is rare in young athletes, as the genetic factors that predispose one to premature disease are uncommon[11]. However, there is an increase occurrence of atherosclerosis in males over 35. Various risk factors can lead to lipid deposition and hardening of the arteries characteristic of the disease (Table 3). In general, moderate exercise is recommended to prevent early death from atherosclerosis[12]. As the study by Quigley reveals, there are a few instances in

which physical exertion in the presence of atherosclerotic disease can lead to sudden death. The mechanism involves fatal ventricular fibrillation provoked by decreased blood flow to the heart due to atherosclerotic coronary arteries and exacerbated by exercise[13]. SCD due to atherosclerosis is anywhere from 10 to 20 times more common than SCD due to hypertrophic cardiomyopathy, coronary abnormalities, or commotio cordis[6]. Yet, the incidence of SCD in athletes with atherosclerosis is extremely low when compared to death from coronary artery disease in the general population. In Ireland, there were 42 SCDs in athletes from atherosclerosis over a 10 year period from 1987 to 1997 compared to 8,000 annual deaths from coronary artery disease during the same time period[14].

Table 3 - *Adapted from Burke AP et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997 (13)*

Major Risk Factors	Minor Risk Factors
Hyperlipidaemia	Male gender
Hypertension	Obesity
Smoking	Sedentary lifestyle
Diabetes	Type A personality (stress) • Impatient • Excessively time-conscious • Insecure • Hostile/Aggressive • Highly competitive
	Elevated homocysteine
	Oral contraceptive use
	Increasing age
	Genetic factors

In the past, there was much debate about implementing athletic screening programs for SCD. It was felt that with the low prevalence of cardiac anomalies, a large number of athletes would have to be screened to identify the single individual who would die suddenly[15]. The likelihood of 'false positives', where tests might incorrectly indicate that someone was at risk, and 'false negatives', where a defect might not be picked up, made screening programs expensive, inefficient and potentially counter-productive[16]. A previous study by Maron, in 2002, estimated the cost of echocardiogram screening of all American athletes for hypertrophic cardiomyopathy to be $2000 per individual [7]. In addition to the high cost, false positive test results could have an emotional toll on athletes and may cause them to unnecessarily give up sports altogether.

Today most cardiologists are in favour of a selective screening strategy. The selective process involves taking the patient history in an attempt to single out those who may be at risk for SCD[18]. Specific questions focus on the family history with regards to SCD, premature death from heart disease, cardiomyopathies, or congenital heart abnormalities. Any past cardiac symptoms such as shortness of breath, palpitations, chest pain, or fatigue would also be explored. A physical exam would then look for abnormalities in blood pressure or heart murmurs. Individuals who are thought to be at risk would then undergo further testing with an echocardiogram and electrocardiogram (ECG).

The success in screening athletes for SCD has been seen in Italy, where all athletes ages 12 to 35 have been screened on an annual basis since 1971[19]. The screening program includes a history and physical examination, exercise and pulmonary function testing, and an ECG. Italy's National Health Service funds the program and has seen a 90% drop in SCD from 3.6/100,000 to 0.4/100,000 in Italy's Veneto region[20]. These favourable results have inspired several physicians and athletic trainers in the United States and Europe to initiate there own screen programs.

CONCLUSION

SCD in athletes is rare but has seen an increase in awareness due to the high profile deaths of several young athletes in the last three decades. Hypertrophic cardiomyopathy, commotio cordis, and coronary artery anomalies are the main causes of SCD in younger athletes, while atherosclerotic coronary artery disease is the main aetiology affecting athletes over the age of 35. The implementation of screening programs for SCD can help identify both young and old athletes who may be at risk. While mass screening for SCD is not appropriate for most countries, a selective screening approach is likely more economical and efficient. As athletic screening programs for SCD start to become more widespread it is hoped that future tragedies may one day be prevented.

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The Link Between Breastfeeding & Asthma - Tenuous or Trustworthy?

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6th Year Medicine

CLINICAL HIGHLIGHTS

- The *Asthma Society of Ireland* reports that the current prevalence of childhood asthma in the Irish population is approximately 15%
- The *World Health Organization* (2002) and the Department of Health and Children in Ireland (2003) recommend breastfeeding for the first six months of life
- 1 out of every 3 Irish mothers breastfeed, at least initially
- High levels of soluble CD14 in breast milk have been suggested to play a pivotal immunomodulatory role in the protection against atopy development
- Breast milk contains Omega fatty acids which are thought to confer protection against atopy by decreasing the synthesis of pro-inflammatory lipid mediators such as prostaglandin E_2

ABSTRACT

Aim: The primary aim of this review was to examine the evidence for and against breastfeeding as a protective factor in the development of asthma in childhood. **Methods:** A literature search was carried out using the PubMed database, yielding 304 papers between the dates of 1-Jan-1999 and 2-Feb-2007. An English language restriction was imposed. Reviewers assessed study quality and extracted data. Relevant data were obtained from Irish, European and international bodies with respect to asthma, the percentage of mothers breastfeeding, and current recommendations for breastfeeding. **Results:** The prevalence of childhood asthma in Ireland is estimated to be 15%, and approximately 30% of children under the age of five have had at least one attack of asthma[2]. Approximately one in three Irish mothers breastfeed, at least initially, and amongst this group 36% did so exclusively[3]. A number of constituents of breastmilk have been proposed to decrease the risk of asthma, including CD14 and omega fatty acids. A 1995 prospective follow-up study reported that exclusive breastfeeding of greater than one month's duration resulted in a significant reduction in respiratory allergy at age seventeen[4]. Of the four randomized controlled trials (RCTs) analyzed in this review, two reported that exclusive breastfeeding, of at least four months duration, significantly reduced the risk of childhood asthma [5,6]. A third RCT found no evident link between breastfeeding and asthma[7], while the final RCT reported that breastfeeding may in fact increase the risk of asthma[8]. **Conclusion:** Given the genetic and environmental variables at play in the phenotypic expression of asthma as a disease, the relationship between breastfeeding and asthma is still somewhat unclear. Four high-quality RCTs yield conflicting results. The World Health Organisation (WHO) and the Department of Health and Children in Ireland both recommend breastfeeding for the first six months of life[9,10]. These evidence-based recommendations consider the benefits of breastfeeding, including reducing the risk of asthma.

INTRODUCTION

The relationship between breastfeeding, asthma, and other atopic diseases has been researched and debated for many years. In 1988, a landmark paper by Kramer described that year as being the "golden jubilee of [this] controversy" [1]. Given the elaborate interplay between genetic, environmental factors and the complex phenotype of asthma as a disease, conflicting studies continue to be published.

The Asthma Society of Ireland reports the current prevalence of childhood asthma in the Irish population at approximately 15%, while an estimated 30% of children under five years of age have had at least one attack of asthma[2]. Recent figures show that approximately 1 in 3 (36.97%) Irish mothers breastfeed at least initially, with greater than 36% doing so exclusively [3].

In 1999, Oddy et al reported the incidence of asthma in children aged six was significantly reduced if exclusive breastfeeding continued for at least the first four months of life[5]. Prior to this, in 1995, Saarinen & Kajosaari reported that exclusive breastfeeding of greater than one month's duration resulted in a significant reduction in respiratory allergy at age seventeen[4]. More recently (2002), Kull et al published a study indicating, yet again, that children breastfed for the first four months of life went on to exhibit less asthma in childhood[6]. Severity and duration of episodes of wheeze have also been linked to duration of breastfeeding[11]. The results of these studies should be carefully balanced with conflicting results from studies conducted by Sears et al[12] and Wright et al[13], which found no evident link between breastfeeding and asthma. In fact, Sears et al reported that breastfeeding may even increase the risk of asthma.

The aim of this review is to explore the evidence for and against breastfeeding as a protective factor in the development of wheeze and asthma in childhood.

Pathogenesis of Asthma and its links with Atopy

The International Consensus Report describes asthma as a "chronic inflammatory disorder of the airways ...[where,] in susceptible individuals, inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment"[14].

The airway wall of patients with asthma is characterized by increased smooth muscle mass, mucous gland hypertrophy and vascular congestion. These changes lead to a thickened airway wall and markedly narrowed airways. The underlying inflammatory process involves the binding of sensitising antigens to Immunoglobulin (IgE) on mast cells. This binding triggers degranulation and the release of inflammatory mediators, such as histamine, proteoglycans and cytokines[15].

According to the Th1/Th2 hypothesis, the immune system is regulated by a balance between T-helper 1 (Th1) and T-helper 2 (Th2) activity[16]. Th1 cells stimulate the type-1 pathway (cellular immunity) to fight viruses and other intracellular pathogens. In contrast, Th2 cells stimulate the type-2 pathway (humoral immunity) by increasing antibody production in response to allergen exposure. In extrinsic asthma, there is a shift towards increased Th2 activity[17]. This shift is associated with atopic sensitization, causing low to moderate airway inflammation[18] and asthma.

Mechanisms by which Breast milk may decrease the risk of developing Asthma

In theory, factors which affect the Th1/Th2 balance by promoting the Th1 pathway or inhibiting the Th2 pathway could infer protection against the development of asthma.

One factor that may influence the Th1/Th2 balance in children is soluble CD14, a constituent of breast milk[18]. CD14, a receptor expressed on macrophages and B-cells, recognizes and binds bacterial cell wall components[19]. After such binding, it initiates signal transduction via the Toll-like receptor 4 (TLR4) resulting in increased secretion of IL-12. IL-12 tends to promote a strong Th1 response[19].

High levels of soluble CD14 in breast milk have been suggested to play a pivotal immunomodulatory role in the protection against atopy development[20,21]. An evaluation of several small scale studies suggested that low soluble CD14 levels in breast milk is associated with development of atopy[22]. However, studies of large populations are lacking.

In addition, breast milk contains Omega fatty acids[18]. Omega-3 (or ω-3) polyunsaturated fatty acids are thought to confer protection against atopy by decreasing the synthesis of pro-inflammatory lipid mediators such as prostaglandin E2 (PGE2)[23]. PGE2 is known to enhance the synthesis of Th2-like cytokines and IgE antibodies as well as inhibiting the differentiation of Th1-like lymphocytes[23]. Hence, by blocking PGE2, ω-3 polyunsaturated fatty acids may favor a Th1 immune response and reduce atopy[23].

Breast milk also contains the ω-6 fatty acids gamma-linolenic acid (GLA) and di-homo-gamma linolenic acid (DGLA), both thought to reduce the risk of asthma[24]. GLA and DGLA can be converted by inflammatory cells to 15-(S)-hydroxy-8, 11, 13-eicosatrienoic acid and prostaglandin E1(PGE1) compounds, which possess anti-inflammatory and anti-proliferative properties[25]. It is notable that neither cow nor soy milk contain significant GLA.

The ratio of ω-3 to ω-6 fatty acids can also affect the Th1/Th2 response. A higher ratio of ω-6 to ω-3 long chain polyunsaturated fatty acids favours a Th1 response, and vice versa[24]. Because breast milk is rich in ω-6 fatty acids (Table 1), the protective effect of breast feeding against atopy might be attributed to its high content of these beneficial fatty acids. In addition, these fatty acids form precursors to various eicosanoids, which also have influences on Th1 and Th2 responses[24].

Table 1. *Polyunsaturated fatty acid composition of mature human milk[24]*

Fatty Acid	Type of Fatty Acid	%wt/wt
Linolenic acid (18:2)	ω-6	10.76
γ-Linolenic acid (18:3)	ω-6	0.16
Dihomo-â-linolenic acid (20:3)	ω-6	0.26
Arachidonic acid (20:4)	ω-6	0.36
α-Linolenic acid (18:3)	ω-3	0.81
Eicosapentaenoic acid (20:5)	ω-3	0.04
Docosapentaenoic acid (22:5)	ω-3	0.17
Docosahexaenoic acid (22:6)	ω-3	0.22
Total ω-6 PUFAs		11.54
Total ω-3 PUFAs		1.24
Total ω-6 PUFAs / Total ω-3 PUFAs		9.31

PUFA: Polyunsaturated fatty acid

Mechanisms by which Breast milk may increase the risk of developing Asthma

It has been hypothesised that exposure to bacteria in early life promotes dendritic cell maturation and stimulates the production of IL-12, provoking a Th1 response[8]. According to the TH1/TH2 hypothesis, this exposure would be expected to decrease the risk of developing asthma later in life.

Exclusively breast fed infants have been found to have lower levels of Gram negative enterobacteria in their gastrointestinal tract [26] and less of a diversity of colonizing species [27]. These infants may experience less dendritic cell maturation and IL-12 production which, consequently, may result in an under-developed Th1 response. In other words, breast fed infants who have had less exposure to bacteria in early life may experience greater Th2 responses and increased risk of asthma.

What if the breastfeeding mother is an Asthmatic?

Breast milk from women with asthma has been found to contain higher levels of IL-4, IL-8 and IgE[13]. All of these compounds are thought to induce sensitisation to allergens, thereby increasing the risk of developing atopy[13].

A prospective, longitudinal study of 1246 newborns, in their first 2 years of life, determined that exclusive breast-feeding was associated with a significantly lower rate of wheeze irrespective of concomitant maternal asthma[28]. However, by age six, exclusive breastfeeding was actually related to a higher rate of asthma in children of mothers with asthma[28]. On the other hand, an Australian study found no statistically significant association between maternal asthma and the development of asthma in breastfed children[29]. Taken together, these studies have been interpreted as displaying an overall protective effect of breastfeeding on the development of atopy and asthma in early childhood, indicating breastfeeding should be encouraged, even by mothers with asthma[7,30].

Does the duration of breastfeeding have any effect?

In one Swedish prospective study, infants breastfed for four months, or more, were less likely than those not breastfed to develop wheeze, asthma, atopic dermatitis and multiple allergic manifestations, at age two years[6]. An additional protective effect was seen in children with a family history of atopy who were breastfed for 6 months[6]. Furthermore, a German prospective study found that a longer duration of breastfeeding decreased the risk of asthma in early childhood[31]. The beneficial effects of breastfeeding might be further supported by high levels of soluble CD14 in breast milk[31].

Selection of studies and extraction of data

Using the keywords 'Asthma' and 'Breastfeeding', a preliminary search on the Pubmed database yielded 304 papers published in English between the 1-Jan-1999 and 2-Feb-2007. The search was subsequently narrowed by selecting cohort studies done in developed countries, and by applying the criteria proposed by Kramer et al[1] for appraisal of the studies concerning the effect of breastfeeding on development of atopy (Table 2).

Table 2. *Kramer Criteria[1]*

(1) **Exposure**
- Non-reliance on late maternal recall of breastfeeding
- Blind ascertainment of infant feeding history
- Sufficient duration of breastfeeding
- Sufficient exclusivity of breastfeeding

(2) **Outcome**
- Strict diagnostic criteria
- Blind ascertainment of outcomes
- Consideration of severity of outcomes
- Consideration of age of onset of outcome

(3) **Statistics**
- Control for confounding
- Assessment of dose-response effects
- Assessment of effects in children at high risk of outcome
- Adequate statistical power

The result was four Randomised Control Trials (RCTs). Two of the studies concluded that breastfeeding had a protective effect in the development of asthma; Oddy et al[5, 32] (Australia) and Kull et al[6] (Sweden). Similarly, two studies concluded that breastfeeding had no such protective effect; Sears et al[12] (New Zealand) and Wright et al[13] (USA).

The studies fulfilled the Kramer criteria but differed in the age of the children at the end of follow-up. The Oddy et al[5, 32] and Kull et al studies conducted follow-up until 6 and 2 years, respectively, while Sears et. al. and Wrighte et. al. until 26 and 13 years, respectively. In addition, Oddy, Kull and Wright studied infants exclusively breastfed for $\geq$4 months, Sears studied infants with duration of breastfeeding of $\geq$4 weeks.

It was decided to compare the outcome of breastfeeding on development of asthma in the samples as a whole rather than concentrating on high risk groups – for example, those with a family history of atopy. The term 'non-exclusively breastfed' was used to include both partial and non-breastfed infants. Diagnostic criteria defined asthma as that diagnosed by a physician, rather than a recurrent wheeze reported by parents, and was applied to all four studies.

Table 3. *Characteristics of 4 RCTs which show the relationship between breast feeding and childhood asthma*

Study	Country	Sample size	Age at follow-up	% EBF developing asthma	% NEBF developing asthma	p value
Oddy et al	Australia	2012	6	7.8	10.6	0.029
Kull et al	Sweden	1246	2	7.7	12	<0.05
Wright et al	USA	1043	13	16.5	12.2	<0.05
Sears et al	New Zealand	1037	26	9	2	0.0008

EBF= exclusively breastfed, NEBF = non-exclusively breastfed

DISCUSSION

The discrepancy between studies is difficult to interpret, with many methodical difficulties to overcome in research of this kind.

The standard measure of statistical significance in most medical research is defined as $p \leq 0.05$. Taking this into account, all the trials reviewed were statistically significant. However, although a $p \leq 0.05$ implies a statistical difference, it does not quantify or qualify whether the difference is a large one or if it is clinically significant.

Asthma is a multifactorial disease. The studies adjusted their data to account for confounding variables such as genetic predisposition, socio-economic status and other environmental factors.

Many of the infants in the studies would have been exposed to cow's milk formula at some stage in their infancy. The potential effect of this exposure on the development of asthma was discounted as negligible in the studies.

To summarize, Oddy et al concluded that introduction of milk other than breast milk increased the risk of developing asthma, while prolonged breastfeeding had a protective effect. Similarly, Kull et al found that infants exclusively breastfed had a lower risk of developing asthma. In fact, they found that even partial breastfeeding (> 6months) was protective, especially in infants with atopic heredity.

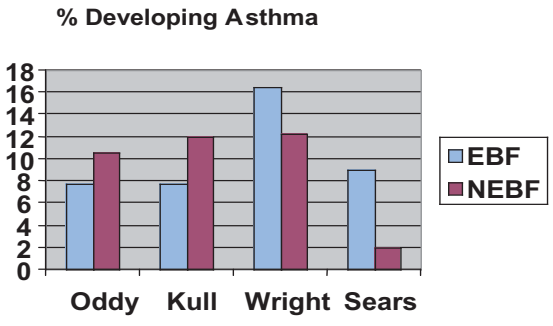

Figure 1: *The relationship between the development of asthma & exclusive/non-exclusive breastfeeding.*

Conversely, Wright et al concentrated on the children of atopic mothers and, in this group, any breastfeeding was found to increase the child's risk of developing asthma. Sears et al found that breastfeeding in all groups (including children with a family history of atopy) was associated with a higher incidence of asthma.

CONCLUSION

Asthma is a condition that affects 15% of Irish children and is characterised by airway inflammation, reversible airflow obstruction and hypersensitivity of airway walls. Breastfeeding is postulated to influence the immunological balance between Th1 and Th2 responses in many ways, some of which may contribute to the atopic sensitisation of airways seen in childhood asthma. Nevertheless, some studies have shown breastfeeding to confer no benefit at all and, in some cases, even an increased risk of asthma in childhood.

In 2003, the World Health Organisation (WHO) published the "Global Strategy on Infant and Young Child Feeding", which recommends exclusive breastfeeding for the first six months of life9. Shortly after this, the Department of Health and Children in Ireland published a press release10 endorsing these WHO recommendations for exclusive breastfeeding in the first six months of life. While these recommendations provide no definitive conclusion to the debate over breastfeeding and asthma they serve to remind readers that there are a myriad of other benefits associated with breastfeeding.

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GlaxoSmithKline - Merit Award Winner

The Role of Bariatric Surgery in the Resolution of Type 2 Diabetes Mellitus

Yasmin Khan

Clinical Points

- In obesity, type 2 diabetes mellitus is largely due to location of adipose tissue and the adipokines released from it. Weight management is usually the primary goal in controlling hyperglycaemia
- With the difficulties and limited achievement presented in non-surgical weight loss, bariatric surgery has become increasingly popular as it is more successful in alleviating obesity-related diseases and obtaining significant weight loss
- BPD, RYGB, VBG, and AGB are the four main bariatric procedures performed today, all of which involves a restrictive and/or malabsorportive component
- Evidence has demonstrated that the exclusion of the hormonally active foregut in BPD and RYGB is far more superior in obtaining glycaemic control than are weight loss and decreased caloric intake alone.
- Changes in the levels of gastrointestinal hormones following foregut exclusion in BPD and RYGB have led to the speculation of their involvement in the aetiology of type 2 diabetes

ABSTRACT

Obesity is a major risk factor for many diseases, most notably for type 2 diabetes. Due to this correlation, weight loss has been a primary objective in managing type 2 diabetes. Current medical weight loss therapies and programs have proved disappointing, presenting an increasingly frustrating problem for the obese and diabetic population. At present, bariatric surgery is the most effective treatment for obesity and type 2 diabetes by inducing significant, long-term weight reduction. The cornerstone for inducing weight loss in these procedures comprises elements of gastric restriction, malabsorption by means of bypassing the foregut, or a combination of both. Depending on the type of bariatric procedure, observation of euglycaemia has been found in 48% to 99% of cases following surgery, therefore proving to be far more superior in treating obesity and type 2 diabetes in comparison to nonsurgical methods. While weight loss may seem like the most reasonable explanation in the improved glycaemic control, several findings have suggested the involvement of other factors. Interestingly, the alterations of various gastrointestinal hormones imparted by the malabsorptive procedures appear to be the dominant feature in the resolution of type 2 diabetes. This article provides an overview of the various bariatric procedures and the physiological mechanisms that contribute to the weight loss and cure of type 2 diabetes after surgery.

INTRODUCTION

Type 2 diabetes, a non-insulin dependent form of diabetes, is one of the most common endocrine disorders that comprise approximately 90% of the 200 million diabetic patients worldwide[1,2]. Obesity is one of the primary factors contributing to the rise in type 2 diabetes and other life-threatening co-morbidities, all of which are growing in parallel with one another[3-5] (Table 1). Initially, this problem was only a matter in the Western world. However, the prevalence of obesity and type 2 diabetes has become much more widespread, rapidly increasing in areas where the conditions have been infrequent [6-8].

Given the association of obesity and type 2 diabetes, effective weight management is a key component in preventing and treating both of these conditions[9]. Several short-term studies have demonstrated that a 5-10% weight loss improves glycaemic control and insulin sensitivity in overweight and obese subjects with type 2 diabetes[10]. A variety of medical (nonsurgical) weight loss therapies exist and have been successful through a combination of diet, exercise, behavioural management and anti-obesity medications[11-13]. However, long-term maintenance of this weight loss has proven to be difficult, especially for individuals with type 2 diabetes as compared to non-diabetic control subjects[14]. This unfortunate outcome may be due to the altered regulation in energy balance due to the effects of hyperglycaemia, or even related to the diabetes therapy itself since most forms of anti-diabetic medications promote weight gain[14]. Furthermore, despite evidence of reduced hyperglycaemia and complications related to type 2 diabetes, the mild weight loss achieved through medical treatment is not substantial enough to return patients to euglycaemia[15].

Bariatric surgery currently serves as the most successful method in achieving significant and long-lasting weight loss. It has proven to be far superior in ameliorating obesity-related diseases in comparison to the short-term mild weight loss obtained by medical treatment[16]. This outcome appears to have a profound effect on type 2 diabetes, completely resolving the disease in 76.8% of

patients, and resolving or improving type 2 diabetes in 86% of patients[17]. Weight loss may seem like the most logical explanation for this outcome; however, there is leading speculation that these improvements may be directly attributed to anatomical changes presented by the operation itself and independent of weight loss. In an attempt to unravel this phenomenon, a closer look will be taken into the obesity and type 2 diabetes relationship, current bariatric procedures, and the mechanism of improved glycaemic control that follows bariatric surgery.

Table 1. *Obesity co-morbidities*

Cardiovascular	***Respiratory***
• Coronary artery disease	• Asthma
• Congestive heart failure	• Sleep apnea
• Hypertension	• Obesity hypoventilation syndrome
• Hyperlipidemia	
	Neurologic and psychiatric
Endocrine	• Migraine headache
• Diabetes mellitus	• Anxiety
• Polycystic ovary syndrome	• Depression
	• Stroke
Musculoskeletal	
• Arthritis	***Gastrointestinal and hepatobilary***
• Gout	• Abdominal hernia
	• Gastroesophageal reflux
Cancer risk	• Nonalcoholic fatty liver diseases
• Colon	
• Prostate	***Hematopoietic***
• Uterine	• Deep venous thrombosis
• Breast	• Pulmonary embolism

Obesity and Type 2 Diabetes

Type 2 diabetes stems from a combination insulin resistance (IR), where the body fails to respond normally to insulin, and the inability of pancreatic beta cells to produce enough insulin to overcome this resistance[18]. While the direct correlation between obesity and type 2 diabetes has always been known, the exact mechanism of the association still remains indefinite.

For a long time, adipose tissue was thought to be an inert, non-active compartment. However, this view has been refuted with the recent discovery of a certain class of hormones released by adipose tissue called adipokines which play a key role in the regulation of appetite and metabolism[19]. Now known as an "endocrine organ," strong evidence exists showing that the amount of adipose tissue may directly contribute to type 2 diabetes by secreting various adipokines, which can also affect the body's sensitivity to insulin[19]. Levels of leptin, for example, are proportional to the amount of fat mass, which explains the elevated levels observed in obesity and the lower levels found upon weight reduction[20]. This adipokine acts by communicating with receptors in the hypothalamus to maintain fat stores at a certain level by means of reducing appetite and increasing energy expenditure[21]. In obesity, however, the effects of leptin are blunted due to the development of leptin resistance[21]. Suppressor of cytokine signalling 3 (SOCS3), an intracellular protein that limits leptin signalling, is likely to play a significant role in leptin resistance[22]. Interestingly, the expression of SOCS3 has been found to also dampen insulin signalling, providing a common point between obesity and type 2 diabetes[23].

The location of adipose tissue is also a large determinant of IR and type 2 diabetes. Visceral fat, as opposed to subcutaneous fat, contributes more to IR and is a prime indicator of health risk[24,25]. The relationship between visceral fat and type 2 diabetes has been demonstrated in the improvement of insulin sensitivity upon the surgical removal of visceral fat in obese Sprague-Dawley rats[26]. Moreover, Gabriely et al. observed different metabolic outcomes upon the excision of adipose tissue from different anatomical sites and found that the most dramatic improvements in insulin sensitivity came from the removal of visceral fat[27]. One of several reasons for this observation is the increased amount of free fatty acids (FFA) due to the enhanced lipolytic activity of visceral adipose tissue. FFA are directly delivered to the liver via portal circulation, acting as a toxic substance and interfering with the regulation of blood glucose levels by resisting the antilipolytic actions of insulin and inhibiting the metabolic breakdown of insulin by the liver[25,28].

Bariatric Surgery: an overview

Nowadays, increasingly more patients are turning towards bariatric surgery as a means for treating obesity. In the United States, the number of bariatric procedures performed has jumped from approximately 5,000 in 1990 to 63,000 in 2002, representing an almost 12-fold increase[29]. While the incidence is not nearly as high, Australia has also seen an estimated 7-fold rise in bariatric procedures from 399 in 1993 to 2992 in 2003[30]. The increasing trend of bariatric procedures can be attributed to the epidemic of obesity, unsatisfactory results obtained from medical treatments for obesity, and the recent advances that have made it a minimally invasive and safe procedure, particularly the application of laparoscopy[5,31].

Table 2 lists the requirements for a patient to become elected for bariatric surgery accordinf to the 1991 guidelines from the National Institutes of Health in the United States[32].

Table 2. *Criteria for Bariatric Surgery*

• Body mass index (BMI) ≥ 40 kg/m2, or BMI ≥ 35 kg/m2 with significant obesity-related disease
• Documented failure of nonsurgical attempt at weight-loss
• Clear understanding of how surgery causes weight loss
• Psychological stability
• Absence of uncontrolled psychotic or depressive disorder
• No active alcohol or substance abuse
• Pre-operative psychiatric evaluation of selected patients

The bariatric procedures performed today can be classified based on their design: intestinal malabsorption, gastric restriction, or a combination of both[3,5].

Malabsorptive operations involve reconstruction of the small intestine by shortening its length or by bypassing certain parts of the intestinal loop. This decreases the functional area of mucosa available for nutrient absorption, and resulting in less caloric absorption and therefore weight loss[5]. Nutrient deficiency is a large downfall of malabsorptive procedures, thus their use has been limited and modified to a great extent in order to reduce these complications[5,33]. Restrictive procedures limit the storage capacity of the stomach by creating small neogastric pouch. The effect of a smaller gastric pouch causes prompt filling by a small amount of food, thereby decreasing meal size, calorie intake, and inducing early satiety, which inevitably results in weight loss[5]. Metabolic complications are less common in purely restrictive procedures since they do not involve alterations in the nutrient absorptive component[5].

Bariatric surgery has greatly evolved from when it was first introduced in the 1950's by Mason, who performed the jejuno-ileal bypass (JIB)[34]. This was a strictly malabsorptive procedure that bypassed most of the absorptive small intestine (Figure 1A). Despite satisfactory results in terms of weight loss, the quantity and severity of the post-surgical complications have led to its abandonment[35]. Based on this experience, a number of bariatric operations have been devised to diminish postoperative complications and to provide patients with more options in achieving weight loss since each operation entails substantially different lifestyle modifications[36,37].

Biliopancreatic Diversion

The biliopancreatic diversion (BPD) was introduced by Scopinaro in the late 1970's and involves a primarily malabsorptive and small restrictive component (Figure 1B)[38]. Weight loss occurs from gastric restriction by a partial gastrectomy, and the diversion of biliopancreatic (bile and pancreatic) juice to the terminal ileum which significantly reduces nutrient absorption. BPD with a duodenal switch was later introduced in the 1990's to avoid the complication of marginal ulcer often seen in BPD alone (Figure 1C). Because this surgery has the greatest amount of anatomical restructuring, the occurrence of peri- and post-operative death is highest in this procedure[5,37].

The mean percentage of excess weight loss (%EWL) following BPD is approximately 75% and has shown to still be maintained at 8 years following the surgery. BPD with a duodenal switch also had comparable weight loss to BPD, but with fewer complications[39]. Substantial improvements in comorbidities have also been observed[40]. In comparison to other procedures, BPD allows patients to eat larger portions since they are left with a greater stomach volume, thereby obtaining weight loss primarily by malabsorption. However, additional therapy is required due to the several long-term complications that exist from its fairly considerable malabsorptive component[38,40]. This procedure is rarely performed nowadays and is mainly reserved for the severely obese (BMI $\geq$ 50 kg/m^2) [41].

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass surgery (RYGB) lacks popularity worldwide, but is the most common bariatric procedure performed in the US[41,42]. Similar to BPD, it incorporates both restrictive and malabsorptive characteristics, but is primarily restrictive. In this procedure, a surgical stapler is used to divide the stomach to form a small, proximal gastric pouch, which is anastomosed to the proximal jejunum in a Roux-en-Y fashion (Figure 2C)[33]. As with all restrictive procedures, the smaller gastric reservoir induced early satiety after a small meal[5], and the Roux-en-Y loop provides a moderate degree of malabsorption by bypassing approximately 95% of the stomach, the entire duodenum, and a small portion of the proximal jejunum[36,37].

By limiting the amount and rate of food ingestion and malabsorption, a 65-75% EWL is maintained at 2 years with a recidivism of 10-15% between 3 and 5 years postoperatively[17]. Durable weight loss has shown to last up to 14 years though[43]. Several long-term risks are associated with RYGB, and lifelong changes must be made in order to avoid complications. Due to the malabsorptive component of the operation, patients need to remain on a high protein, low fat diet, and take nutritional supplements to avoid metabolic deficiencies[37,44]. In addition to avoiding foods that may inhibit normal emptying of their gastric pouch, patients are advised to keep sweets to a minimum due to the risk of dumping syndrome. This is a common side effect that occurs with rapid emptying of the gastric pouch directly into the jejunum especially with the ingestion of carbohydrates, causing an osmotic overload which leads to nausea, palpitations, cramps and abdominal discomfort[45]. This unimpeded load can also contribute to hypoglycaemia by rapid release of insulin from the pancreas. Other complications include stenosis of the gastrojejunal anastomosis and marginal ulcers[37].

Vertical Band Gastroplasty

Vertical band gastroplasty (VBG) is one of two purely restrictive operations currently performed for weight loss. VBG consists of vertically partitioning the stomach by a surgical stapler to create a small proximal pouch, and placing a synthetic ring around the stoma for reinforcement (Figure 2A). This procedure is much easier to perform that BPD and RYGB, and post-surgical complications are less since digestion and absorption remain normal, thereby lacking nutritional deficiencies[37]. However, vomiting, band erosion, and increased severity of gastroesophageal reflux can occur[45].

In VBG, weight loss results from restricting the capacity of the stomach and thereby limiting food intake. Studies show a 30-50% EWL within the first 1-2 years, which is much lower than BPD and RYGB[39]. Due to instances of patient non-compliance, long-term results are also disappointing. Patients are often able to accommodate gastric restriction by eating more frequent small meals and calorie-dense foods[45]. It is to no surprise that an 80% failure rate is observed 10 years following VBG[46]. At this time point, only 20% of patients maintain a durable weight loss of at least 50%[46]. For this reason, VBG has become increasing unfavourable.

Adjustable Gastric Banding

Adjustable gastric banding (AGB) is a purely restrictive bariatric procedure and is one of the most frequent procedures performed in the bariatric realm, particularly in Europe and Australia[30,37]. Its popularity is most likely due to its minimal invasiveness, absence of anastomoses, adjustability and reversibility[31]. This approach involves placing a hollow silicone band around the upper part of the stomach, resulting in a small proximal gastric pouch that fills quickly and empties slowly (Figure 2B). The process of weight loss is similar to that of VBG, but has a further advantage of being able to modify gastric restriction by a simple, non-invasive office procedure that involves injecting or withdrawing saline solution from the hollow core of the band that is accessed via a subcutaneous access point (Figure 3). No other operation has this flexibility of tuning gastric restriction to meet the patient's needs[31]. Risks associated with the surgery are significantly less than all other bariatric procedures (30) and are mainly related to the band itself, specifically band slippage, band erosion into the stomach, and movement or leakage of the subcutaneous port[5,36].

With a good follow-up program, patients have been reported to lose up to 50-60 %EWL[17,47]. However, there is considerable variation of this result. Both Europe and Australia have reported excellent outcomes, which is contrary to the inadequate weight loss results in the US. Some studies in the US have reported a %EWL of 18% 3 to 18 months following surgery, prompting, in several cases, band-removal due to insufficient weight loss[48]. In a study by Chevallier et al., an observed %EWL of 50% at 2 years among French subjects has been documented[49]. Furthermore, Fielding et al. reported a 62% EWL in Australia[50]. The difference in the US results may be due to experience since it was only recently approved in 2001, whereas AGB has been an accepted and commonly practiced procedure in Europe and Australia since the 1980's[30,37,51]. Moreover, it is unclear if the poor results are due to differences in diet, lifestyle, or compliance with patients in the US[37]. AGB is slowly increasing in the US though, and their results have been getting increasingly similar to those achieved in Europe and Australia[52,53].

Mechanism of Diabetes Resolution Following Bariatric Surgery

Bariatric surgery not only induces significant and durable weight loss, but several cases have shown the improvement and complete resolution of type 2 diabetes. The degree of improvement of type 2 diabetes varies with operative procedure. According to a meta-analysis by Buchwald, diabetes was completely resolved in 99% of patients who underwent BPD and duodenal switch, 84% of RYGB patients, 72% of VBG patients, and 48% of AGB patients[17]. While the precise mechanism for this dramatic effect still remains unknown, hypotheses include decreased weight and food intake, and in the case of BPD and RYGB, bypass of the foregut[54].

At first, the level of type 2 diabetes resolution was thought to be attributed solely to the weight loss imparted by the bariatric operations. This may be true, given the relationship between adipokines and type 2 diabetes. However, several observations suggest that factors other than weight loss are likely involved. This is especially evident in BPD and RYGB which involve bypass of the hormonally active foregut. In the case of these two procedures, multiple studies have demonstrated an impressive observation of euglycaemia and normal insulin within days after surgery, long before any major weight loss has occurred[43,55]. Furthermore, the remission of their type 2 diabetes was far superior than that observed in those who had lost weight through diet alone[56]. Similar observations have also been made in a study by Hickey et al. where a group of obese women who underwent RYGB were compared to a control group of obese women. Both groups were matched for weight, age, percentage of fat, and BMI; and had maintained that weight for at least six months, thereby excluding weight loss as a variable. Despite similar characteristics, the surgical group ended up having lower fasting plasma glucose and higher insulin sensitivity compared to the control[55]. This suggests that in the case of BPD and RYGB, which both involve bypass of the foregut, there may be other factors that work alone or in conjunction with weight loss that contribute to the full remission of type 2 diabetes.

Decreased food intake has also been postulated to play a role in the remission of type 2 diabetes. If this were true, then VBG and AGB would be just as effective as BPD and RYGB because their surgeries also result in significantly reduced food intake. However, in comparison to RYGB, their effect in reducing hyperglycaemia is far inferior and evidence is lacking in the long-term cure of type 2 diabetes[57]. Furthermore, the eating capacity of BPD patients is much larger in comparison to all other bariatric procedures, yet glucose levels still remain under control[58]. Therefore, despite significant weight loss and decreased food intake imparted by VBG and AGB, the absence of foregut exclusion in these procedures suggests that this may be the very underlying feature that contributes to the superior control of glucose and insulin levels observed in BPD and RYGB[59].

One of the most convincing experiments that led to the discovery of the direct effect of gut exclusion on type 2 diabetes remission was a bypass surgery performed on Goto-Kakizaki rats by Rubino and Marescaux. With no significant change in food intake or weight loss, full remission of diabetes was observed[60]. Sugerman et al. also observed more profound changes in gut hormone profiles and greater resolution of type 2 diabetes following RYGB in comparison with VBG, which does not involve bypass whatsoever[61]. Furthermore, in a comparison between surgical and non-surgical subjects who were matched for BMI, surgical patients were found to have a noticeable decrease in both leptin and fasting glucose levels. Increased insulin sensitivity and decreased food intake were also observed[55]. These results suggest that the improved control of type 2 diabetes may not be secondary to weight loss or decreased caloric intake, but rather to the anatomical reconstruction from BPD and RYGB, specifically bypass of the hormonally active foregut.

Role of Gastrointestinal Hormones

Gastrointestinal hormones are responsible for controlling appetite and have a profound effect on insulin action and secretion upon the ingestion of food. The anatomical changes in the gut as a result of BPD and RYGB, in particular bypass of the foregut, may be a dominant factor in the beneficial effect on type 2 diabetes and weight loss by direct modification in the levels of these hormones.

Based on this observation, gastrointestinal hormones have been a new focus in elucidating the mechanism of type 2 diabetes resolution following bariatric surgery. Pories et al. hypothesized the possibility of a hormone in the foregut that causes type 2 diabetes by producing an abnormal signal from the gut to the pancreas that results in hyperinsulinaemia, inevitably leading to IR[56]. If type 2 diabetes is a disease of the foregut, then bypassing this region afforded by BPD and RYGB might explain the improvement and cure of type 2 diabetes following surgery in both of these cases.

Exclusion of the foregut may also induce the production of pro-insular hormones by expediting the delivery of nutrients to the hindgut[55,56]. Glucagon-like-peptide 1 (GLP-1), for example, is one of the most classic gut hormones known to have a potent effect on insulin secretion. GLP-1 is secreted in the ileum after food ingestion to facilitate nutrient absorption by inhibiting gastric emptying, food intake and insulin secretion. All of these characteristics have been observed upon the intravenous or subcutaneous administration of GLP-1 in subjects with type 2 diabetes[62]. The low levels found in patients with type 2 diabetes may possibly be attributed to this gut hormone[62]. Several studies have observed the rise in levels of GLP-1 after BPD and RYGB along with the improvement and resolution of type 2 diabetes[63], which dramatically increase GLP-1 levels and insulin secretion as a result, leading to the improvement of type 2 diabetes[64,65].

In review, the characteristic bypass involved in BPD and RYGB appears to be a key factor in euglycaemia in bariatric patients with type 2 diabetes. While this effect is known to be attributed to the changes in gastrointestinal hormones, their exact mechanism of action still remains in a grey area. Consequently, further investigation needs to be carried out to elucidate their function and possibly identify any other gastrointestinal hormones that may be involved in glucose metabolism, along with how physically excluding the foregut affects these hormones.

CONCLUSION

Type 2 diabetes is one of the most prevalent co-morbidities associated with obesity. With the number of cases of both increasing worldwide, much of today's focus remains on finding an effective prevention and treatment for these two conditions. Weight loss has been the mainstay of medical therapies for type 2 diabetes, but results have shown to be inadequate in achieving significant and long-term weight loss. Many have turned towards bariatric surgery as a result, which has proven to be a much more successful method in providing consistent and durable weight loss. Furthermore, a large proportion of bariatric patients with type 2 diabetes have been cured as a result of the operation. Even though all bariatric procedures result in improved weight loss and diabetes control in comparison with conservative methods, BPD and RYGB offer superior weight loss and resolution of diabetes. With weight loss aside, bypass of the foregut involved in both of these procedures seems to be the main characteristic in inducing this dramatic effect, resulting in a change in the level of gastrointestinal hormones that may have a vital component in the aetiology for type 2 diabetes. More studies are needed to fully elucidate the mechanism to gain a further understanding of the pathophysiology of type 2 diabetes and as their potential as drug targets for anti-diabetic medications.

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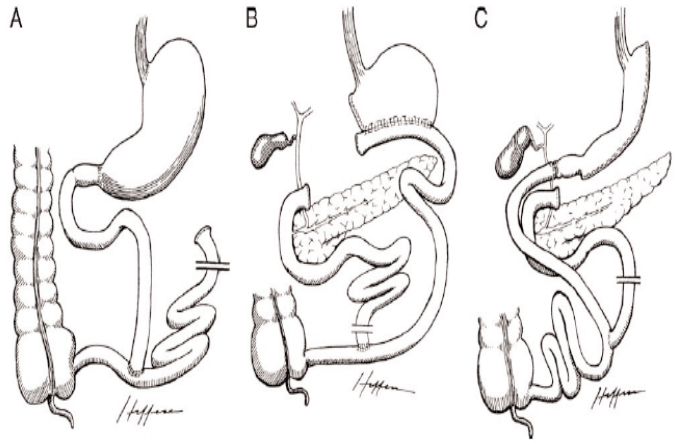

Figure 1. A - Jejunoileal bypass; B - Biliopancreatic diversion; C - Biliopancreatic diversion with duodenal switch. (32)

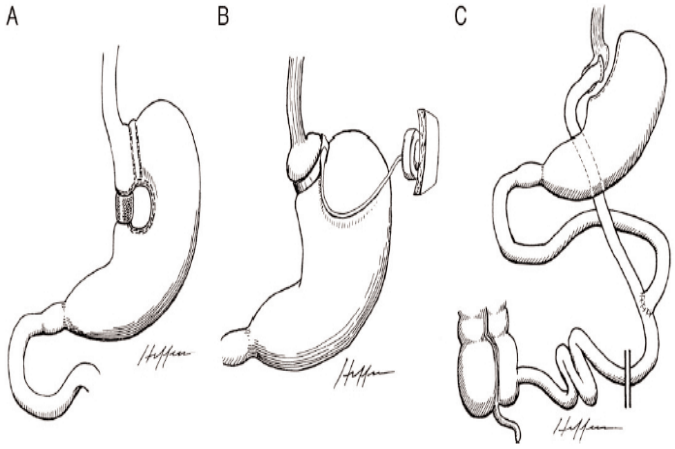

Figure 2. A - Vertical banded gastroplasty; B - Adjustable gastric banding; C. Roux-en-Y gastric bypass. (32)

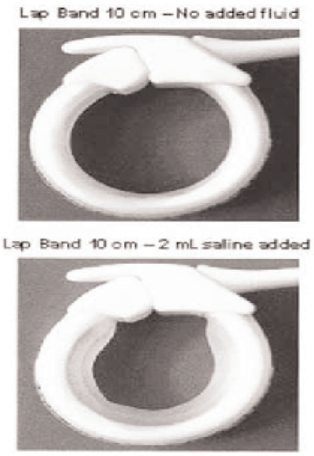

Figure 3. One common type of band used in adjustable gastric banding, with and without added saline. Note the decreased area within the band (30).

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Leo Pharma - Merit Award

Treatment of edentulous patients using implant supported mandibular overdentures improves quality of life

Sarah Enright
5th year Dentistry

CLINICAL POINTS

- The standard of care for the edentulous patient has been the provision of a complete denture, however a large proportion of patients have problems with the retention and stability of the mandibular complete denture
- Pre-prosthetic surgery(PPS) has a history of poor prognosis
- The McGill Consensus states that the two implant mandibular overdenture should be considered as a first choice standard of care
- Compared to complete dentures and PPS, improvements have been demonstrated in areas such as patient satisfaction, nutrition, and quality-of-life
- Quality-of-life is a useful method to demonstrate treatment success, however, the use of individualized quality-of-life measures may prove more relevant in the future

INTRODUCTION

An overdenture (OD) is defined as a prosthesis that covers and is partially supported by natural teeth, tooth roots, and/or dental implants[1].

Tooth loss is a serious life event[2]. According to the WHO criteria edentulism is a form of physical impairment,[3] the loss of all teeth causes a disability for most people who wear conventional dentures (CD) as they may have difficulty in performing two essential tasks; eating and speaking.

Quality of life (QOL) is defined as an individual's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns[4]. The impact of health and disease on QOL is known as health-related QOL. Another dimension of QOL is Oral health-related QOL. This is defined as an individual's assessment of how the following affect his or her well-being: functional factors, psychological factors, social factors, and experience of pain or discomfort in relation to orofacial concerns[5].

QOL is established as an important outcome for evaluating the impact of disease and for assessing the efficacy of treatments[6]. QOL in denture wearers is measured by socio-dental indicators. Locker defined these indicators as; measures of the extent to which dental and oral disorders disrupt normal social role functioning and bring about major changes in behaviour such as an inability to work or attend school, or undertake parental or household duties[7]. Therefore QOL affects denture wearers with regard to patient satisfaction, nutrition and psycho-social aspects of life. QOL is, however, adversely affected by tooth loss.

The sequelae of tooth loss

The effects of tooth loss are two-fold which may affect the patient psychologically and clinically.

Psychologically, edentulism has been quoted as having characteristics of a chronic illness as it is incurable and functionally and physiologically disruptive[8]. Reduced self confidence, taboo and the feeling of premature ageing have also been reported by patients[8].

Clinically the effects of tooth loss are important. Alveolar bone resorption could be considered as a pathological condition and can pose a prosthodontic dilemma for the restoration of the edentulous mandible. There has been extensive research regarding this aspect and its clinical sequelae. Tallegren reported that the mean decrease in anterior mandibular ridge height was 4 times greater then that of the maxilla[9].

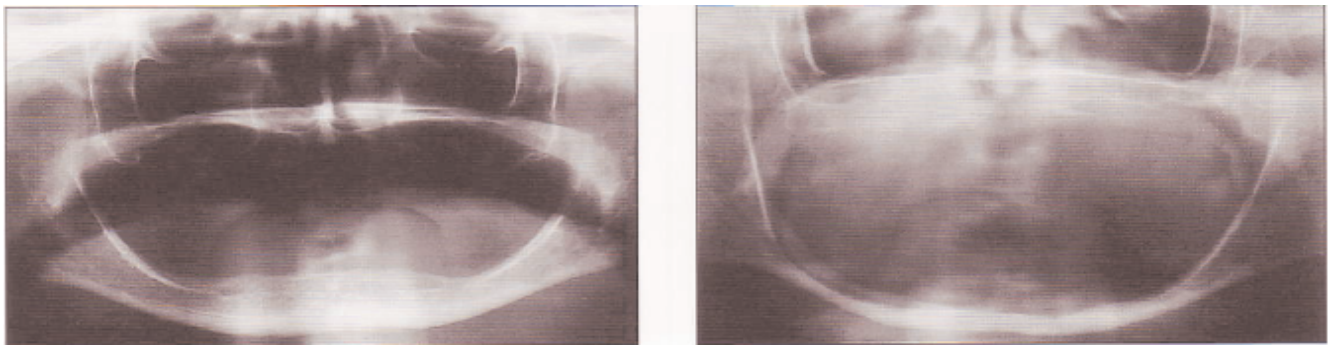


Image 1 & 2: Progression of alveolar bone resorption in the mandible over a 15 year period[10]

Crum and Rooney found that retaining mandibular canines and providing an OD resulted in 0.6mm of alveolar bone loss[11]. Provision of a CD resulted in 5.2mm of bone loss[12]. Therefore preserving teeth and providing an OD can preserve bone not only local to the teeth, but also in adjacent areas.

Alveolar bone loss can be reduced by the provision of implants; studies have shown that implant-supported mandibular overdentures (ISMOVDs) can preserve bone height in areas where the implants are located[12]. Mericske-Stern also concluded that there is a higher probability of success in the mandible when ODs are supported by implants rather than tooth roots[13].

Treatment modalities for the edentulous mandible

Treatment modalities for the restoration of the edentulous mandible include: a mandibular CD, pre-prosthetic surgery (PPS) with a mandibular CD, an ISMOVD and an implant-supported fixed bridge.

Much of the literature focuses solely on the comparison of the ISMOVD with the CD, with or without PPS. This section will, therefore, compare and contrast these treatments by analysis of current literature and, thus, show how the restoration of the edentulous mandible with an ISMOVD should be considered as a first choice standard of care.

The classic treatment for the edentulous mandible is a mandibular CD. However the pattern of bone loss associated with the CD can result in the denture-bearing area becoming compromised. Redford demonstrated that more then 50% of CD wearers have problems with the retention and stability of their mandibular CD14. When the patient experiences poor denture retention and stability, patient satisfaction, confidence and comfort will suffer.

The rate of resorption of the mandibular alveolar bone is greater than that of the maxilla[9]. PPS (ridge augmentation or vestibuloplasty) has, therefore, been advocated in certain clinical circumstances. There is, however, mixed long-term success rates associated with PPS; complications and morbidity are also associated[15, 16].

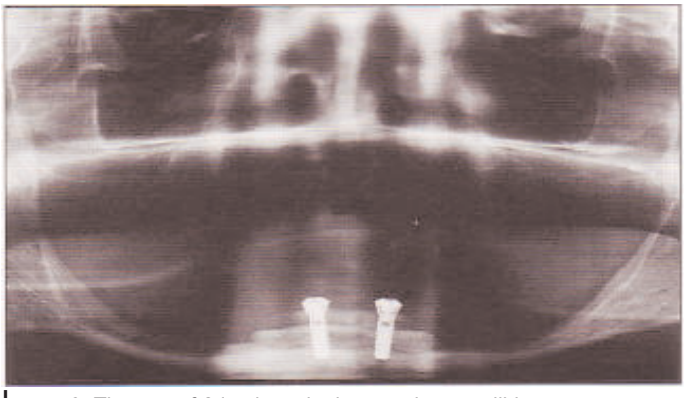


Image 3: The use of 2 implants in the anterior mandible to support an OVD[10]

A symposium was held at McGill University where a panel of experts concluded that a 2 implant overdenture (OVD) should be considered as a first choice standard of care for the edentulous mandible[17].

The ISMOVD has been investigated since 1987, with Van Steenberghe[18] being one of the first authors to propose the placement of 2 implants in the mandible to support an OVD. Within 52 months, a 98% success rate was achieved[18]. Albrektsson et al. have argued that a state of almost, "restitution ad integrum," can be achieved with dental implants[19].

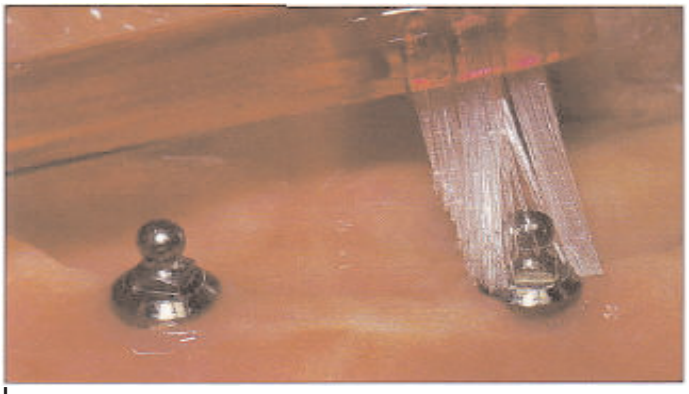


Image 4: Patients should be instructed to remove their prosthesis at night. A soft single-tufted brush is indicated to keep attachments free from plaque and calculus[22]

ISMOVDs require frequent maintenance, especially during their first year[20]. Attard et al. concluded that the cumulative survival rate of the OD was 100%, at 15 years, with the longevity of this prosthesis being 10.39+/-5.59 years[20]. Relines were required every 4-5 years for both the OD and opposing CD[20]. However, less after-care was associated with surface treatment of the implants and the use of Dolder bars[21]. Patients must be informed that regular maintenance will be required. Also, this will give the clinician the opportunity to regularly review the patient and detect possible pathology which may otherwise have adversely affected them.

QOL-Patient Satisfaction

It is accepted in the literature that satisfaction in denture wearers depends upon the ability of the patient to chew and speak, and also on the appearance of the prosthesis[23, 24, 25]. Berg et al. found that 66% of patients were dissatisfied with their CDs due to discomfort, sub-optimal retention and fit, and/or pain associated with the lower CD[26, 27].

Many studies have assessed patient satisfaction with ISMOVDs[27-36]. Wismeijer et al. carried out a randomized controlled trial (RCT) where patients were provided with ISMOVDs with either ball attachments, an interconnecting bar, or 4 interconnected implants[37]. Sixteen months after treatment almost all of the patients were satisfied with treatment irrespective of attachment system used[37].

Boerringter et al. assessed patient satisfaction in a RCT[31]. This study compared the CD with an ISMOVD. Satisfaction was measured with a validated questionnaire which assessed: esthetics, retention, comfort, and function of the upper and lower denture. The majority of the ISMOVD group (85%) had a score of 8 or more (score 1=very dissatisfied, score 10=very satisfied)[31]. Results showed that the ISMOVD group was more satisfied 1 year post-treatment. Dissatisfaction in the CD group was due to the poor retention of the lower CD; only 27% were satisfied post-treatment[31]. The design of this study shows a high degree of validity, however, a longer follow-up is required.

The first prospective RCT with a 10 year follow-up was carried out by Raghoeber et al.[37]. Patients were randomized as follows: a) CD (control group); b) PPS with a CD; and, c) ISMOVD. Within 1 year, the PPS and ISMOVD group experienced better chewing ability than the CD group. The PPS group was satisfied in the short-term. The ISMOVD group experienced long-term satisfaction (10 years.)

From the above evidence it can be concluded that patient satisfaction is improved with the provision of an ISMOVD compared to a CD, with or without PPS. Patients were not only satisfied in the short-term but also at a 10 year recall.

QOL-Nutrition

As tooth number decreases, mastication is more difficult; patients are also more likely to practice forms of food avoidance and dietary restriction.

Morais et al. revealed that patients provided with an ISMOVD reported an increased ability to bite, eat and chew, without losing their dentures, 6 months post-treatment[38]. This group also showed improvements in anthropometric data and blood nutrient data. Serum albumin concentration increased by 1.4g/l (a recognized indicator of good general health) [39]. Serum B12 concentrations also increased. These findings, however, should be supported by a larger RCT with a longer follow-up in the future.

The process of dietary restriction amongst edentulous patients has also been studied. Allen and McMillan found that subjects who received ISMOVDs altered their food choices, including, "hard to chew foods"[40].

From the literature it can be concluded that the ISMOVD offers the patient significant improvements in nutritional status. The ISMOVD will not necessarily result in the patient eating a more balanced diet of their own accord. Thus, in order to allow patients benefit most from their improved masticatory function, dietary advice should be given[40, 41, 42].

QOL-Psychosocial effects of ISMOVDs

Blomberg stated that teeth do not function just as a part of the masticatory system; the oral region is also a speech and a psycho-sexual centre[43]. The success of denture treatment is not solely based upon functional parameters.

The effects of denture wearing on social activities have been studied by Heydecke et al. who carried out a 2 month follow-up RCT comparing CDs and ISMOVDs[44]. Many studies use scales such as the Oral Health Impact Profile (OHIP) to measure QOL. Unlike the Soical Impact Questionnaire (SIQ), the OHIP does not take into account social or sexual activities. This study concluded that the ISMOVD had a positive effect on social activities 2 months post-treatment. Conversely, the instability of the CD was shown to adversely affect social activities and interpersonal relationships. Unease in interpersonal relationships was reduced by 32% 2 months post-treatment with the ISMOVD[44]. The SIQ scale showed a high level of reliability. However a longer follow-up period is still required.

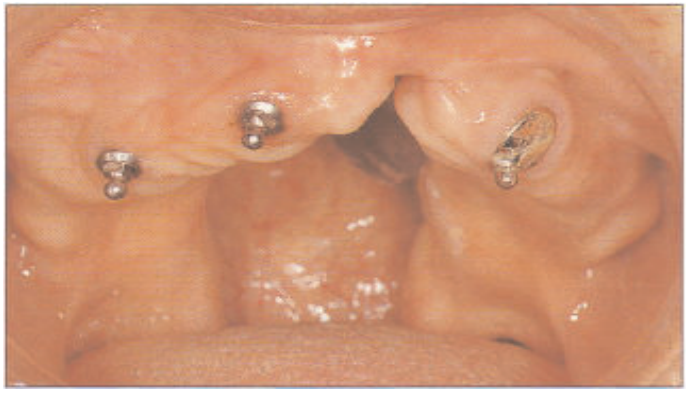
The effect of the ISMOVD on social activities was also studied by Melas et al. who carried out a retrospective cohort study based upon the Oral Impacts on Daily Performances (OIDP) sociodental indicator[45]. The OIDP measured psycho-social variables such as: smiling, clear speech, emotional status, social contact and, "going out." Results showed that patients with ISMOVDs were more satisfied with the comfort of their dentures. Sizable percentages (66%) of CD wearers were dissatisfied with the comfort of their prostheses[45]. The main limitation of this study was its design. The groups were also not comparable on the basis of age; however, from previous literature it seems that there is no relationship between age and patient satisfaction[46]. Thus, age is unlikely to have confounded the above results.

From the literature, patients restored with ISMOVDs experience less discomfort and improved psychosocial function. Studies with longer follow-up periods are required.

DISCUSSION & CONCLUSIONS

The standard treatment of the edentulous patient has, for many years, been a CD. Many CD wearers have significant problems in adapting to their mandibular prosthesis. The widespread use and abuse of denture adhesives is a good indication that these prostheses are inadequate in relation to retention and stability. CDs have many disadvantages such as: continual ridge resorption with fibrous replacement, instability of the CD, displacement of the CD, variable levels of acquired muscular control, changes in facial support, reduced masticatory efficacy and emotional distress from tooth loss[47]. PPS has also been associated with poor results15, 16.

Treatment of the edentulous mandible with an ISMOVD has been advocated by Mericske-Stern in elderly patients, who require stabilization of their mandibular CD, and in patients with congenital or acquired maxillofacial defects which require oral rehabilitation[48].



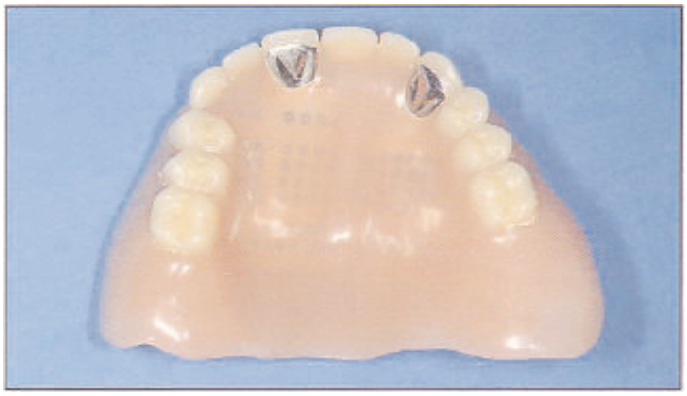


Image 5 & 6: Placement of implants in a 90 year old patient with a cleft palate, right: Fabrication of a complete denture with full palatal coverage and obturator[10]

However a panel of experts (The McGill Consensus)[17] agreed due to overwhelming evidence that the 2-implant OD should be considered as a first choice standard of care for the edentulous mandible[17].

As with any treatment modality, the commitment to after-care and maintenance is vital if the OD is to be successful. The patient must be advised of this and reviewed regularly. As previously mentioned, this may give the clinician the chance to regularly review the patient and detect possible pathology which may then be treated in a timely fashion.

From the evidence presented in this paper it can be concluded that the edentulous patient restored with an ISMOVD (rather than with a CD with or without PPS) experiences more satisfaction with their prosthesis, improved masticatory ability and nutrition, along with improvements in psycho-social aspects of life. However, prospective randomized studies with longer follow-up periods are required. It can also be concluded that patients restored with ISMOVDs will experience improvements in QOL with regard to oral health-related QOL.

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A Look at Oral Cancer - Specifically Tongue Cancer

Una nic Ionmhain
5th Year Medicine

Clinical Points

- Oral cancers arise between the lips and the anterior pillar of the fauces. They are the 6th most common malignancy worldwide. 90% being SCCs
- Risk factors include, smoking, alcohol, family history and premalignant lesions
- A thorough history and physical are necessary. A 3 week history of a mouth ulcer and cervical lymphadenopathy should be treated as urgent.
- Management is multidisciplinary. Depending on staging, treatment is surgical or with radiotherapy. A dissection of the neck may also been necessary.
- The 5 year survival rate for lesions less than 2cm, without lymph node involvement, is 80%. This is reduced by 50% with cervical node involvement. Therefore, focus should be on early diagnosis and preventative measures

ABSTRACT

Oral cancers are defined as neoplasms arising between, and including, the lips and the anterior pillar of the fauces. Ninety percent of carcinomas arising in this region are squamous cell carcinomas[1]. These cancers are managed in differently depending on their staging and location. Many are silent lesions, presenting at a late stage, making treatment difficult and resulting in a low survival rate with this form of cancer. It is very rare in the West, with over 4500 cases diagnosed a year in the UK[2], in contrast with Asia where it accounts for up to 40% of cancers[3]. Treatment is either surgical or radiotherapeutic, depending on the staging of the tumours. Prognosis is significantly worse in later stages, with a 45% to 65% survival rate when metastatic nodes in the neck are present[4].

Case History

Patient A, a gentleman in his sixties, presented to the outpatient department with a five month history of a tongue lesion that was initially noticed on a routine dental examination.

He reported constant throbbing pain confined to the right side of the tongue. The pain worsened while eating. The lump had enlarged over the past 5 months and he reported some dryness of the mouth, halitosis and an intermittent tingling sensation in the lower jaw, neck and shoulders.

There was no dysarthria, dysphagia or odynophagia. He had no history of mouth ulcers, leucoplakia, erythroplakia or lichen planus. He reported no alteration in sensation or taste, no bleeding, no hoarseness or dysphonia. He denied weight loss, fatigue, loss of appetite and was not aware of any palpable lumps specifically in the head and neck region.

Patient A had a significant smoking history of 22.5 pack years. He ceased smoking 30 years ago. He consumes 28 - 36 units of alcohol a week. He had no family history of malignancy.

Investigations

He was referred for biopsy which diagnosed squamous cell carcinoma (SCC) of the tongue. Subsequent investigations, including CT and MRI, did not reveal any metastatic spread. He was admitted for laser excision of the lesion and selective neck dissection.

ENT Examination

Mouth: The right lateral border of A's tongue showed a palpable raised, irregular, poorly demarcated swelling, approximately 1 - 2 cm in size. The lesion was non ulcerated and non necrotic. It was not bleeding and had no rolled edges. There was no evidence of leukoplakia, lichen planus, erythroplakia or other premalignant lesions. All mucosal surfaces were intact. There were no other palpable masses on the base of the tongue or the floor of the mouth.
Ear and Nose: No abnormality
Neck: There were no palpable or visible lumps or cervical lymphadenopathy.
All cranial nerves were intact.
All other systems were normal on examination.

Summary

In summary, Patient A is a gentleman in his sixties admitted for partial glossectomy and selective neck dissection to resect a lateral tongue SCC and a clinically node negative neck.

DISCUSSION

Definition

Oral cancers are defined as neoplasms arising between, and including, the lips to the anterior pillar of the fauces.[1] More than 90% of carcinomas arising in the head and neck are SCCs.[1] Others include salivary gland tumours, lymphoreticular, haemopoetic, primary bone tumours, malignant melanomas, sarcomas and metastatic disease.[5, 6] Clinically, the most common sites include the buccal mucosa, the floor of the mouth, the lateral and ventral tongue and the retromolar trigone.[3]

Epidemiology

Oral cancers are rare in the UK and Ireland. Over 4500 new cases (2003) are reported each year in the UK.[2] The incidence is rising primarily amongst men.[7] In combination, oral and oropharyngeal are the 6th most common malignancy globally.[5] Although the incidence is low in the West (2-4%), in Asia, it ranks amongst the three most common malignancies,[8] with an incidence of up to 40% in some parts of India.[3] It is most commonly seen in the male population over 60 years of age.[7] There have, however, been recent reports of increasing incidence amongst females and young males in Europe and North America without a history of alcohol or tobacco use.[3] The disease carries significant morbidity and mortality. In Britain, over 1400 people die of oral SCC every year.[2] Survival is very dependent on staging. Late presentation results in late treatment and poor prognosis.[8]

Risk Factors

The best documented risk factor for oral neoplasia is smoking tobacco. Approximately 75% of patients have a smoking history.[6] In Asia and the Far East, there is a large association with smoking PAN (a combination of betel vine, areca nut, lime and tobacco) or the practice of reverse smoking - with the burning end in the mouth.[3,5] Alcohol, especially brown spirits, acts synergistically with tobacco to increase the risk of cancer.[9]

Other risk factors include genetic susceptibility, poor oral hygiene and oral mouthwashes[9], and a poor diet low in vegetables and anti oxidants. Some newer studies have linked HPV 16,18 and 33 with increased risk of developing the disease.[10]

There seems to be no doubt that significant associations exist between premalignant lesions and oral cancers, although the precise nature of these associations continues to be debated. Leucoplakia is defined as "a white patch or plaque that cannot be characterised clinically or pathologically as any other disease" [3]. Its appearance varies. Previously thought to carry a high risk of malignant change, it is now thought to be between 3-6% 10. The risk increases with the age of the patient.

Erythroplakia, a very rare velvet red lesion seen in the mouth, on the tongue or soft palate of patients in their sixties to seventies, is more significantly associated. On biopsy, 70 - 90% are invasive carcinoma, carcinoma in situ, or dysplastic.[11] The incidence of malignant change is 17 times higher in erythroplakia than leucoplakia, and the lesion must be excised.[3] Other associated conditions include chronic hyperplastic candidiasis, oral submucosal fibrosis, syphilitic glossitis, and sideropenic dysphagia.[3] The role of lichen planus is still debated. It is worth noting that many of these premalignant lesions do regress and are not necessary for the cancer to occur. [3, 11]

Clinical Features of Tongue Cancer

Most patients with tongue cancer are asymptomatic or may be misdiagnosed by their health care provider and given anti fungal treatment, steroids or mouthwash. This often results in late diagnosis.

Of the tongue cancers:

- 51% occur on the lateral margin of the middle third of the tongue
- 25% occur in the posterior third
- 20% in the anterior third
- 4% occur on the dorsum.[3]

They manifest in different ways:

- An exophytic and ulcerated lesion
- An ulcer within a fissure,
- An area of superficial ulceration in which muscle infiltration has occurred
- A leucoplakia associated lesion
- An asymptomatic atrophic depapillated area.[3]

Intermediate lesions present as a persistent fixated ulcer and there may be lymphadenopathy. Late lesions manifest as large indurated crater ulcers with granular floors and rolled margins. There may be pain, numbness or parasthesia. Pain may be severe and radiate to the neck and ears.[5] Lesions may be bleeding and necrotic.

Lymph node metastases are common in later stages. Fifty percent of patients have palpable nodes at presentation. There is early nodal spread in this form of cancer, so that 12% of patients who present with a lump in the neck show no evidence of a primary cancer.[3] Any patient with an ulcer present for more than three weeks and cervical lymphadenopathy should be considered at risk.[6]

Investigations

An extensive history and examination must be carried out with emphasis on dates and onset. The physical examination must include examination of the inner and outer oral ring and mucosa, the area behind the fauces pillar, the parotid duct and the tongue. The floor of the mouth and base of tongue must be palpated. Bite

should be assessed, and relevant cranial nerves examined.[9] A thorough examination is needed as there is a high association with synchronous and metachronous primaries occurring in the aerodigestive tract in up to 15% of patients[12] . The neck must be palpated thoroughly for cervical lymphadenopathy. A full clinical work up should include liver function tests, as head and neck cancers may metastasise to the liver. A full blood count, urea and electrolytes, coagulation screen, along with a group and hold should be obtained if considering surgical management.

The lesion must be biopsied under local or general anaesthetic depending on its size. The most suspicious part of the lesion must be taken and some normal adjacent mucosa, taking care not to biopsy bleeding or necrotic areas as this will interfere with the findings. Some lesions are examined under anaesthetic so the patient can be in a relaxed state permitting thorough visualisation. If there is a neck lump, a fine needle aspirate must be performed.

Due to the high incidence of synchronous and metachronous tumours in the oropharyngeal area, endoscopic investigations are commonly preformed. These investigations include laryngoscopy, oesophagoscopy and bronchoscopy and any suspicious lesion will be biopsied. A dental examination must be performed with focus on dental hygiene, dentition status and the integrity of the mandible. This is paramount if considering radiotherapy.

Radiographic investigations should include plain film x-rays of the oral cavity to assess involvement of the mandible. A chest x-ray should also be obtained in view of metastatic spread and also as part of the preoperative assessment. A CT (which will show metastatic spread) and MRI (which will illustrate the soft tissue infiltration) should be obtained. Radionuclear scanning is of little value in primary oral cancer - obvious clinical disease usually precedes any findings. An ultrasound can be obtained of the abdomen when investigating liver metastases [3,5,6]. After radiographic scanning, the patients stage increases in 30% of cases. Staging follows the TNM or TANIS guidelines1 (Table 1).

Table 1 - *TNM Staging in Oral Cancer*

Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0, T1-3 N1, and M0
Stage IV	T4 any N, T1-3 N2-3, any T any N M1

Management

Management is multi disciplinary, involving an oncologist, otolaryngologist or maxillofacial surgeon, plastic surgeon, radiotherapist, pathologist and speech and language therapy. Treatment of choice is dependent on several factors. Can the lesion be easily excised or should radiotherapy be considered? There is debate with regards to which is the better of these, especially as cure rates are similar in the intermediate stages T1, T2, T3.

Surgery is indicated in lesions which are easily accessible and also if there are multiple primaries. Larger masses with bony involvement are treated with extensive surgery. Any involvement of cervical lymph nodes requires surgical resection with either a radical neck dissection or selective neck dissection. Surgery is also indicated in a patient with a history of recurrent tumours and previous irradiation. As radiotherapy may induce malignant change at a later stage in a younger patient, surgery is preferable. Histologically, adenocarcinomas and melanomas are radioresistant, therefore surgery should be considered. The grade of SCC does not influence management as much, except with verrucous carcinoma, in which radiotherapy may make it more anaplastic.

Radiotherapy is indicated in primary treatment. It can also be used to debulk the cancer or to prevent recurrences. It should also be considered in older patients who are poor surgical candidates.[3] Post operative combination radiotherapy and chemotherapy are offered in advanced disease.[13] If radiotherapy is being provided, a dental evaluation must be sought to decide if teeth in the field of irradiation need to be extracted. This generally involves
1) removal of teeth with advanced caries
2) teeth with advanced periodontal involvement
3) teeth with periapical pathology.[14] Chemotherapy is mainly used in palliation.[5]

Surgical Management

Treatment of choice is intraoral excision. The size of the lesion dictates the surgical management. If less than a third of the tongue is involved, it is excised without any grafting and allowed to heal by secondary intention3. Excision is performed with a 2cm margin. For partial glossectomies a CO_2 laser is frequently used as it decreases post operative pain, oedema and scarring. If the lesion is greater than 2cm, a hemiglossectomy is done. If there is more extensive involvement a major resection is necessary, involving radial or pectoral flap reconstructions.

Neck Management

There is significant evidence of early micrometastatic spread to the cervical lymph nodes with oral cancers. They are thought to be present in up to 20% of

node negative patients. Survival of patients is far lower once cervical lymph nodes become involved. Therefore, there is a debate about whether a selective neck dissection should be done on a patient with a clinically node negative neck.

Retrospective studies have shown an improvement in survival with an elective neck dissection versus later surgical salvaging. Some centres employ a watch and wait policy, but problems occur with patients failing to attend follow up. Block dissection does carry negligible mortality and acceptable moribidy. Failure to control neck metastases results in death.

However it is worth noting that it is no guarantee against recurrance and lymph node removal might make recurrance of the primary or a second primary more difficult. Prospective studies have shown little statistical difference in survival between those treated with neck dissection and those that were monitored.[3] To guarantee the removal of all positive nodes, one would have to remove 96% of them.

The neck is divided into five levels. The neck dissection can be radical or more recently modified or selective where the internal jugular vein, sternocleidomastoid and the accessory nerve are preserved. Depending on the extent of the spread in the neck these levels are dissected. Squamous cell carcinoma of the tongue drains to levels I and II initially with involvement of the inferior groups in the chain as the disease spreads.[4] In clinically node negative necks, only the supraomohyoid levels (levels I - III) are dissected.[15] Prospective studies show control rates in selective neck dissection that are similar to modified radical neck dissection with N0. If there is involvement of level IV, then post operative radiotherapy is offered which improves regional control.[16] Oral cancers rarely present with bilateral nodal involvement. If there is an unusually large primary, it is treated with external radiation. A bilateral neck dissection is performed with a radical dissection done on the ipsilateral side and selective neck dissection on the contralateral side.

Expected Course / Prognosis

Prognosis is largely dependent on stage of presentation. In spite of surgical advances, the overall five year mortality has changed little over the past few decades. Without nodal involvement the 5 year survival rate is 80%. Survival rate is reduced to between 45% and 65% in patients with metastases, depending on the extent of nodal involvement4. Many of these patients have co-morbidities related to their drinking or smoking habits which lead to a worse prognosis.

Prognosis is worse with lesions which arise posteriorly in the oral cavity as they tend to be diagnosed later and have rich lymphatic drainage which favours early metastatic spread. Females tend to have a better prognosis as they tend to be diagnosed and treated earlier than their male counterparts. This is a reflection of the fact that females attend the dentist more regularly than males. Age also influences prognosis as patients become less able to withstand surgery and radiotherapy with advancing age. As previously explained, these patients are at risk of additional primary neoplasms in the aerodigestive tract. This occurs in up to 25% of patients who have oral cancer for greater than 3 years and in up to 40% of those that continue to smoke.[5] Additional complications of treatment must also be noted, such as infection, bleeding, a reaction to the general anaesthetic and an overall reduction in the patient's quality of life secondary to the resection. Radiotherapy is associated with an increased risk of oral mucositis, xerostomia and osteoradionecrosis.

Prevention

Primary prevention can be achieved by advising cessation of smoking and moderation of alcohol intake. Smoking cessation has also been shown to be associated with regression of pre-malignant lesions such as leucoplakia. Other suggestions include the improvement of diet and the use of antioxidants to prevent recurrance or prevent malignant transformation. However, this has not been proven. Among the reasons cited for poor prognosis in oral cancer are poor knowledge and education about the presentation of oral cancer. Screening and educational campaigns have also been suggested, however, in the west oral cancers are rare so that screening may not be cost effective.

Dental care has a major role in the prevention and detection of oral squamous cell carcinoma. However, lower socio-economic groups and other groups such as the elderly rarely attend for dental care. Therefore, in the interest of preventive care, regular dental check ups should be encouraged by offering financial assistance to patients within such groupings.[8]

Poor referral rates from doctors are believed to arise from a failure to recognise signs and symptoms. This is thought to be partly due to the lack of emphasis on oral examination in medical school. Therefore medical student education is an important target in prevention.

CONCLUSIONS

Oral Cancers are extremely rare in Ireland, but they carry significant rates of mortality. As early diagnosis vastly improves the 5 year survival rate, more time should be spent educating patients and health care professionals about the condition. Doctors should be aware that it is a clinical necessity to examine the oral cavity and be aware of the possibility of oral malignacy.

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Into the Silence: Working with Autism

Aimy Abdullah

Clinical Points

- Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders characterised by a triad of distinct features:
  (i) impaired development of social interaction skills;
  (ii) limited ability in speech and non-verbal communication;
  (iii) presence of typical, restricted, repetitive and stereotyped patterns of behaviour.
- Individuals with autism experience the world differently; approach with understanding and respect.
- Autistic individuals report the following problems:
  (i) altered sensitivity to stimuli;
  (ii) limited ability to concentrate on more than one sensation at a time;
  (iii) emotional distress;
  (iv) poor communication skills;
  (v) less socially-orientated priorities
- When interacting with autistic individuals, remember:
  (i) their right as a person to demand equal, mutual respect
  (ii) their thinking processes usually differ from others
  (iii) their limited capacity in filtering and interpreting external stimuli; as well as limited ability to pay attention to more than one stimulus at a time
  (iv) they may seem to have varying degrees of empathy
- Remember to consider the needs of the parents and caretakers; provide extra support for them.

INTRODUCTION

"I can remember when I tuned out, I would just sit and rock and let sand go through my hands. I was able to shut the world out… You have got to keep autistic children engaged with the world. You cannot let them tune out."

Dr. Temple Grandin was diagnosed with autism when she was 3 years old, and has since fought to prove that being labelled 'autistic' is not a 'death sentence to achievement or productivity in life'[1]. Presently an Associate Professor at Colorado State University and a renowned professional designer of humane livestock facilities, she is arguably the best living proof that the reclusive characteristics of autism can be modified and reshaped. The outcome of Autism Spectrum Disorder (ASD) is dependent on both early detection and intervention, with about one third of autistic persons being able to attain some degree of independent living[2]. Having the crucial guidance of a mentor who can recognize abilities and encourage interests can make a world of difference to autistic children. However, before anyone can tap into their inner potential, there is a wall of communication and understanding difficulties which has to be breached.

ASD is a group of neurodevelopmental disorders which are usually diagnosed in children before the age of 3. ASD classically presents with a triad of features:
a deficit in the general development of social skills (withdrawal, lack of interest in peers);
limitations in the use of interactive language (speech as well as nonverbal communication);
the presence of typical, restricted, repetitive and stereotyped patterns of behaviour (preoccupation with rituals, repetitive motor mannerisms)[3, 4,5].

In 1943, Kanner identified a syndrome he labeled "autism"[6]. Since then, no single cause has been identified for the development of this disorder. A genetic basis has been suggested by studies on twins. It has been shown that there exists a higher incidence of recurrence among siblings[7]. In addition, some reports have suggested a possible association with genetic conditions such as fragile X syndrome[8], tuberous sclerosis[9] and Down syndrome[10]. Neurotransmitters, such as serotonin, have been implicated in the development and expression of autism[11]. Other possible contributing factors in autism development include infections[12], defects in protein processing[13], errors in metabolism, immunological dysfunction, lead poisoning, and fetal alcohol syndrome[14].

Many intervention strategies are available for children with autism. Pharmacological management is currently used only to control and help reduce behaviour problems[2]. The main focus of early interventions were psychological and behavioural. Interventions include sensory integration, touch pressure intervention, auditory integration training, behavioural interventions, comprehensive interventions or relative-based intervention[15].

The incidence of ASD has gradually increased over the past few decades. This is due in part to changes in the diagnostic criteria, the development of the concept of a

wide autistic spectrum, and growing awareness among parents and professional workers. Other factors include the development of specialist services, as well as the possibility of a true increase in ASD incidence[16]. Between 1,200 and 2,000 children and young adults are affected by ASD in Ireland; increasing by nearly 100 new cases per year[17]. Recent studies in Ireland have found an incidence rate of 15 per 10,000 births[17].

Children with ASD frequently pose a great challenge to caregivers and health professionals alike. Breaching the communication and comprehension barrier can be undeniably frustrating. This essay intends to explore this barrier from the point of view of both the individuals affected by autism and the people they interact with, namely the care workers and members of staff involved in their daily lives. Recommendations for creating more positive approaches and practices are also submitted. In addition, the provision of outside support for carers and parents are considered, as their level of tolerance and stress may have a compelling effect on the efficacy of communication and, ultimately, the overall progress and prognosis of the child.

Breaching the communication and comprehension barrier

The First-Hand View of Autism

To understand the autistic experience one must begin to understand what it is like to have ASD. Many theories of autism have emerged though none accurately conveys the first-hand experience of this condition. Patients' histories, and indeed autobiographies, can impart details essential in establishing an 'insider's' perspective of ASD. A study by Olney was conducted using this method[18]. Three autobiographies[19,20,21] were selected as core texts to identify key themes from among 13 chosen to be analyzed. The themes were then compared and contrasted with the remaining books, identifying common points and disagreements

The study succeeded in pinpointing several key themes, concerning difficulties and experiences with sensation, attention, affect, communication, and social interaction. People with ASD experience the world differently and should be approached with openness and respect[18]. In order to understand ASD, strengths must be considered as well as deficits[22,23]. The findings are listed in Table 1.

Children with ASD experience frustration at being unable to communicate. Dr. Grandin once admitted that as a child, she "screamed because it was the only way (she) could communicate" [24]. She firmly believes "in lots of early intervention with little kids". The following excerpt from her book outlines the intervention she recommends;
"get them talking if possible and get them interacting with people… It is important to look at the functioning level of the child, because what's appropriate for nonverbal patients is totally different from what's appropriate for very mild Asperger's patients… they do need to learn social skills, but there's so much emphasis on social skills, there's no emphasis on career development…I get social interaction through shared interests at work, like talking about how to build something or solve a problem in animal behavior. Now that's really interesting to me; social chit-chat's not"[25].

Table 1 - *Key themes identified by persons with autism regarding their condition[18].*

Key Themes	Findings
1. Sensation	Persons with ASD can experience altered sensitivity to stimuli. Sensation may be fragmented, variable, increased, or decreased. This can result in what Williams [25] has termed "shut down". Sellin [26] described it as an acute panic attack brought about by sensory and emotional overload.
2. Attention	Those with ASD seemed to have limited capacity to give attention to more than one sensation at a time [27,28]. Both a dissociation between auditory and visual attention, and an inability to rapidly shift attention have been observed [23,28]. This can lead to either social and cognitive delays [28]; or proficiency and the development extraordinary talents [19,21,29].
3. Emotion	Not being able to easily interpret events and filter stimuli often result in distress and anxiety [20,22]. However, many also reported experiencing acute, intense pleasure while engaging in a particular activity which interests them [19,21,25,27,30].
4. Communication	Individuals with ASD may face difficulty interpreting situational nuances, fail to consider context, and have trouble sifting the essential from the trivial [31,32]. Other dilemmas include initiating conversations, and specific problems with receptive and/or expressive communication [19,22,33,34,35].
5. Social Interaction	Several authors disclosed that they did not feel the need for a mutual relationship in the same way that non-autistic individuals do, however, they sometimes desired companionship [23,36]. This is made complicated by the difficulties in understanding and producing the subtleties of both spoken and physical language, such as facial expressions and tone of voice.

The Carer and Staff Member's Point of View

The staff involved in caring for children with ASD play a significant role in their lives. Not only do they affect the child's future success and outcome, they are looked upon to deal with any challenging behaviours which could arise in the present. At times, individuals may become violent and harmful, not only to others but to themselves as well. They might appear to be resistant to all forms of treatment. Staff members are held responsible to handle and deal with such situations professionally, with most managing via both practical and factual knowledge[37].

Emotional responses to challenging behaviours can affect the staffs' reaction to those behaviours and also play a fundamental role in maintaining their psychological well-being. A study by Jahoda and Wanless[38] found that when faced with these situations, the majority of staff members had a significantly intense emotional response. Nearly one half of the staff believed that the individual's aggression was directed at them personally[38]. The majority of staff

members described patients in negative terms, and mentioned that their first impulse had been to confront them[38]. A qualitative study by Hastings and Brown[39] on the possible predictors of staff member's emotional reactions revealed several factors which may influence their vulnerability to experiencing negative emotions in reaction to challenging behaviours. These factors include their beliefs about the cause of the behaviour, lower level of competence and poor prior behavioural knowledge. Surprisingly, staff with formal qualifications also reported more negative emotional reactions when compared with those without[41].

Staff behaviour can sometimes be unsupportive and discouraging. The enormous workload burdened upon staff members may cause them to spend less time interacting with those under their care; and make the quality of these interactions poor[40]. Self-report studies reveal that most of the staffs' responses to challenging behaviour were that of the nature which reinforces such adverse behaviours[40]. Occasionally they may act in a paternal manner, dominating over the individual's rights to decide over his own body and liberty, claiming that 'doctor knows best'. The paternalistic "typecast" notion that people with ASD do not have the capacity to exercise their right to self-autonomy can be seen as discrimination of the disabled, and even a breach of human rights.

This ethical issue has been brought forth to the European Court of Human Rights in 2004 by HL, a man with autism who was held for 5 months in a psychiatric hospital without his consent[41]. Because of his autism, he was deemed to lack the capacity to exercise autonomy, and so, despite the existence of the Mental Health Act, he was detained. . The Court ordered the British Government to pay £20,000 compensation to HL for breach of his human rights. This ruling could potentially affect thousands of people with learning disabilities and dementia, who cannot consent to or refuse treatment. The Government should allow patients without the capacity to consent to be protected by the same safeguards set up to defend the rest of society against wrongful, forced admissions to hospitals.

Recommendations for creating more positive approaches and practices

Anyone who works with individuals with ASD must be able to grasp the concept that every human is unique. Personal interaction style differs from person to person. However, experienced staff members and carers have several distinct qualities which create positive interpersonal communication. General approaches and strategies can be used but they must, however, be tailored according to individual needs[42].

Before engaging with persons affected by ASD, one must carefully consider their strengths and weaknesses. One must also always remember that underneath the layers of skin and sinew lives a person who has equal rights and demands equal respect just like any other. Several basic points on interaction to bear in mind when one is working with children and adults with ASD include:

1. The right of a person with ASD to demand equal respect.

People with ASD should be treated with the same respect shown to others[41]. Conventional etiquettes still apply; mutual respect is still regarded as the seed from which a fulfilling relationship will grow and flourish.

Be sensitive when you are talking to or speaking about those with ASD[42]. Don't refer to them as "an autistic". They are affected by autism; they are not autism *per se*. People with gastric ulcer or Parkinson's disease are not referred to as, "he is a gastric ulcer" or, "she is Parkinson's", and autism is no different.

One should also limit and avoid using psychiatric terminology as much as possible, unless it is for psychiatric or medical analysis. Terms such as obsessive, compulsive, ritualistic, or delusional can be quite inaccurate and judgmental, and should be replaced with less incriminating terms like "highly liked activity, or intensely focused interests"[42]. Where terms may be misunderstood, observed descriptions of the behaviour could be used.

Some people prefer to discuss cases while the patients themselves are not present. This is because no one truly knows the extent to which patients with ASD understand or their emotional reaction to what is being discussed, they simply may or may not be able to express themselves quite as well as other people[42]. If it is unavoidable, and the patient is within hearing range, one must remember to include them in the discussion even if they might not contribute anything to it.

2. ASD implies different thinking processes.

People with ASD usually have comparatively different cognitive processes. They are more inclined to think in a channeled, serialized manner ("monotropism") and are also less likely to be able to think in general terms ("closed thinking")[43].Children, in particular, tend to think in literal terms[43]. They often fail to interpret subtle expressions used in everyday life. One must therefore be patient and understanding when talking to them as it may take them some time to digest and formulate a response to what one is saying to them.

Individuals with ASD may have difficulty understanding or complying with requests[18]. One should avoid *asking* a series of questions and should instead *tell* the patient what to do directly using concise, concrete language. For instance, rather than saying, "Where are you supposed to be right now? What do you see the other people doing? What is it time to do?", one could say, "Lucy, it's time for painting. Come to the table."[42].

Furthermore, people with ASD may not readily differentiate a question from a statement. Use a different tone of voice and communication cues when conveying a message and when asking a question[42]. For instance, if a question has been asked, patiently wait for an answer and try to look like one is anticipating the answer. One must not be too quick to add more verbal information and non-verbal cues when individuals with ASD seem to be taking a long time in processing what one has said to them. Extra information may just confuse and serve as a distraction to their train of thought [42,43].

3. People with ASD may have limited capacity to filter external stimuli as well as limited ability to concentrate on more than one stimulus at a time.

Individuals with ASD may be hindered from social interaction by their limited capacity to filter sound, touch, visual input, and movement. They may not be able to concentrate on more than one stimulus at a time. Too much stimuli may lead to frustration and agitation[18].

When working with another staff or family member, it is important that the patient is not put in a situation in which he/she needs to divide his/her attention[42]. Try not to talk simultaneously or repeat each other verbally. Rather, try using appropriate cues such as gestures, physical prompts, written or visual signs to reinforce the statement said by the other person. One must also try not to interrupt active interaction.

4. People with ASD have varying degrees of empathy.

Although empirical evidence show that individuals affected by ASD are lacking or have diminished empathy[44,45,46], one must understand that this is only from a psychological and psychiatric point of view. It would be inaccurate to assume that individuals with autism do not have feelings for others. They may just be unable to express the right body language or they may not fully comprehend the need for the expression[18,47].

Provision of extra support for carers and parents

Parents and carers of children with autism face unique challenges everyday. Sometimes these challenges may get to be too much for them to handle. Anxiety and frustration arising from carrying the burden day in and day out could potentially lead to more serious psychopathology. A little understanding and support may alleviate some of the stress.

Possessing a more positive sense of one's own efficacy ("self-efficacy") and belief in one's own competence ("self-competence") has long been linked with better psychological well-being and less psychological distress[48]. This optimistic view of oneself has also been known to hold great influence on parenting behaviors and reduced parenting stress[48]. Adopting coping strategies which have a positive impact on self-efficacy increases the likelihood of more positive and adaptive outcomes[50]. Examples of such coping strategies include actively seeking social support and reframing experiences to make them more positive. It is important to turn parents away from using escape and avoidance as coping mechanism as it has been shown to be associated with higher levels of stress in the family[51].

Provision of adequate social support to the family helps to reduce stress and depression[52]. Having a good social network aids in the family's adjustment and relieves fathers' psychological distress[49]. Support can be sought from either family, friends, support groups or counsellors. People who will be caring for the patients may be experiencing different dilemmas: parents may feel incompetent and guilty towards the child; siblings may feel embarrassed or jealous at the attention given to the child; close relatives may not know how to handle the child. In these cases the help of a professional counselor may be of great benefit[53].

Respite care may provide a much needed break for over-stressed families. Burke and Cigno cited that it 'removes temporary strain and crisis in the family unit…Once parents used respite facilities, they were unequivocal in their praise…feeling that they could not survive without them'[54]. Many may only consider respite care as a last resort. This may be because parents tend to initially feel guilty at wanting to place the child into institutional care and are afraid to cause the child distress. The use of respite care indicates a realistic acceptance that some parents could not continue to care for their child without any rest or pause[34].

Some parents may be distressed or 'hurt' as a result of the aloof nature of autism. Spontaneous and impulsive physical 'displays of affections', such as cuddling, are usually rejected and even feared by the child. Touch Therapy Programme[55] or massage intervention[56] therapy have been shown to help. Children who have had these therapies are generally more relaxed, able to tolerate more physical contact, and even expresses the desire to initiate massages at home. Parents reported feeling both physically and emotionally 'closer' to their children[56]. These therapies open a communication channel between parent and child, thus working to strengthen the emotional bonds between them.

CONCLUSION

As the incidence of ASD in Ireland increases, there is a need to become more competent with its management. Many in our profession are ill-equipped when it comes to having the skills required to work with autistic individuals, including medical students. ASD presents a special kind of challenge. Children with ASD may experience difficulties

in sensation, attention, affect, communication, and social interaction on a wide continuum, some of which may be hard to comprehend. The barrier of silence, or indeed, chaotic tantrums could merely be a coping mechanism due to an inability to filter and comprehend verbal and non-verbal communication. To the child with ASD, the world is an alien place which may seem very confusing and hostile at times. It is a challenge then to coax them out of the comfort of their inner worlds and get them to be a part of the real world. Patience and understanding of their condition is the key to helping these children communicate and understand the world.

Patience, dedication and respect are cardinal attributes required in creating positive practice. Though the way one would approach these children differs from one person to the next, several key ideas have been identified which are generally practicable when interacting with people with ASD. One should treat them with as much courtesy and respect as one would any other person. Considering the way they think is simply different from others and that they have limited capacity in filtering and interpreting external stimuli, one should be more tolerant when interacting with individuals with ASD, and not be too quick to blame them if they seem to be taking too much time responding. Always remember that, although these individuals may seem to have varying degrees of empathy, they are not without emotions. They feel what everyone else can feel, but they may simply be unable to express it.

Frustration and stress in parents, carers and staff members may lead to counter-productive attitudes, which is why additional support may be warranted. The psychological well-being of Staff affects the care and therapeutic progress of the individuals. The social stigma and stereotyping of autism, as well as emotional factors, may affect the judgment of the professional staff and increase family stress. Being able to trust one's own competence and manage stress effectively can allay depression and psychological instability, as well as prevent burnout. Strong social support is of considerable importance, and this includes having supportive friend and family, and counseling if need be. Families will also benefit from the occasional respite care. Special therapy, such as the Touch Therapy, can increase the child's tolerance to physical contact, and thus enable the parents to be more physically affectionate with their children.

Dr. Grandin once said 'I would think in an ideal world, you don't want to have people who can't talk, but on the other hand, you definitely don't want to get rid of all of the autism genetics because if you did that, there'd be no scientists. After all, who do you think made the first stone spear back in the caves? It wasn't the really social people.'

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