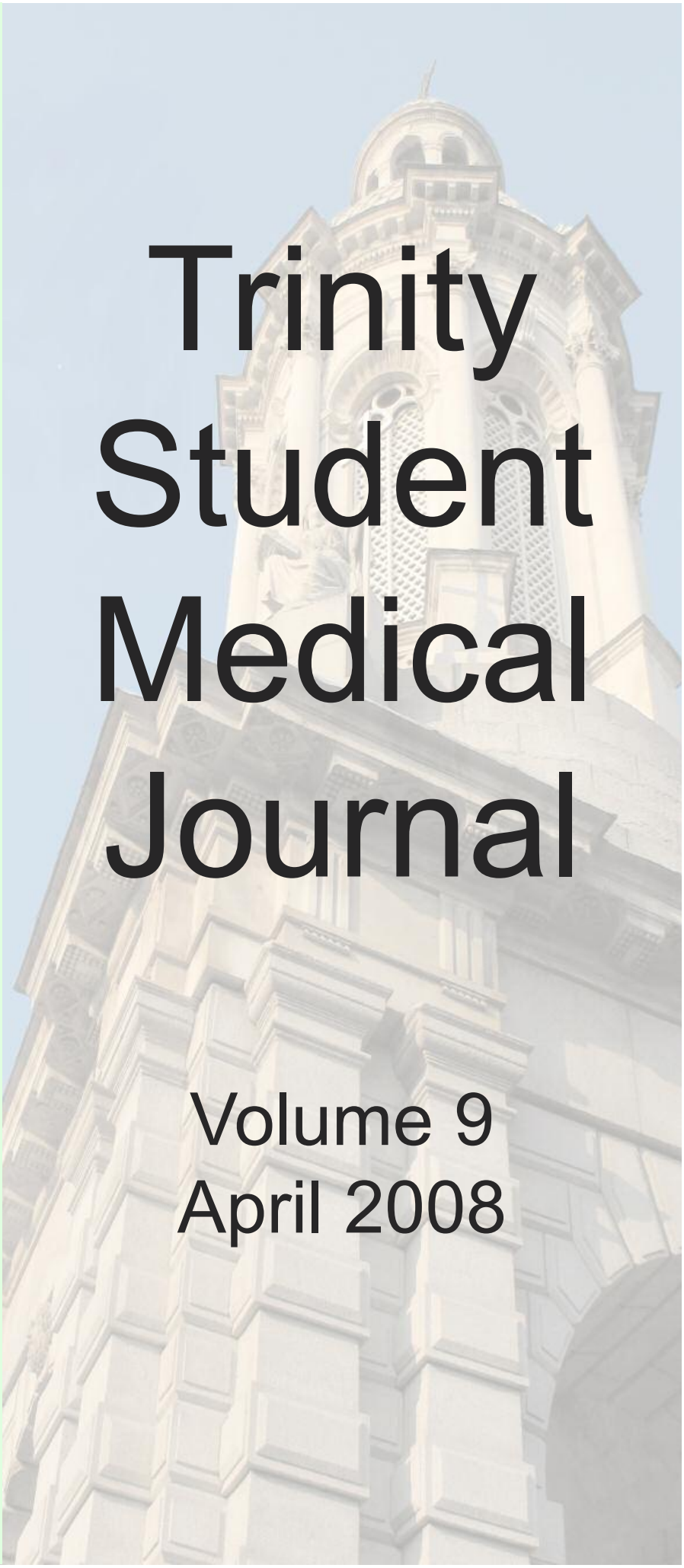

Trinity Student Medical Journal

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The Trinity Student Medical Journal is intended to provide an inclusive vehicle for students to communicate current medical research, opinions and thoughts to other students, faculty members and faculty of affiliated hospitals and institutions. We publish articles relating to many aspects of medicine including scientific research and clinical experience. Articles are accepted from students in medicine and other relatd fields, as it is our view that medicine is the meeting point of many disciplines. The aim of the journal is to provide a medium that is responsive to the rapidly changing face of contemporary medicine, and is able to grow and expand as rapidly as the subject.

All published articles are decided by a panel of editors drawn from the medical student body of Trinity College, Dublin. All submissions are chosen by a double-blind method, with all identifiers removed from submission until final selection by the editorial committee is completed.

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Cover picture: A computed tomography image of an intestinal malrotation, taken from the case report titled "32-Year-Old Man with Abdominal Pain, General Malaise and an Inability to Eat: A Case of Intestinal Malrotation" by Katie O' Sullivan, 6th year Medicine, T.C.D. The image is courtesy of Dr. Iqbal Kahn, Senior Lecturer in Surgery, AMNCH.

Inside cover picture: The campanile, T.C.D., courtesy of Patrick Ryan 6th year Medicine, T.C.D.

A Message From The Director

Dear Colleagues,

It's with great pleasure that I welcome you to the ninth edition of the Trinity Student Medical Journal. The TSMJ is written, edited and produced solely by medical students of Trinity College, Dublin.

The TSMJ was initially established to provide medical students with a vehicle to have their research and clinical experiences published. This was quickly expanded upon to offer the same opportunity to all students in the Faculty of Health Science and other biomedical fields. This decision has clearly added to the journal's success and is unmistakably reflected in the broad base of this year's submissions.

We are reliant on students to make this journal a success, whether submitting an article or working tirelessly as part of our committee. Firstly, I would like to thank all the students that put forward an article for publication, whether they were successful or not. We acknowledge the valuable time and effort you have spent writing and researching these pieces. With such a large volume of submitted articles it is, unfortunately, impossible to print them all but I encourage those that did not succeed to try again next year.

I would also like to express my gratitude to those that volunteered to work as part of our committee. It would be impossible to produce such a high quality journal without the staggering amount of time and effort they have sacrificed. As the TSMJ committee changes and develops, new faces appear and old ones move away. I would like to thank last year's committee, especially Michael Ednie, Jared Butler and Padraig Casey for making this transition as smooth as possible. I would also like to thank the extremely patient people at D.U. Publications for their help.

Previous directors of the TSMJ have highlighted how important sponsorship is for the survival of our journal. This year will be no different. I wish to thank all the patrons of the TSMJ, both old and new for their contributions. I would also like to thank our corporate sponsors for investing in this valuable resource.

As we move towards our tenth edition, our thoughts turn to the future. With this in mind, our marketing team have established links with libraries used by students in Ireland in the aforementioned fields to distribute copies of this year's journal. Building on this, we hope to have a stronger submission rate from outside Trinity College next year.

Best wishes,

David Foley

Director 2008

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W.M.D.s

Weapons of Mass Destruction or Whirlpools, Mohs and Doha agreements?

Though occasionally medics or scientists may encounter weapons of mass destruction during their careers, it's far more likely the W.M.D.s that they will face will consist of Whirlpools, Mohs surgeries and Doha agreements. The ninth issue of the TSMJ features a taste of W.M.D.s for your reading pleassure, saving those who wish to find them a potentially lengthy or embarrassing hunt.

W.M.D.s highlight the massive spectrum of medicine that is constantly developing and broadening, creating specialisations, sub-specialisations and sub-sub-specialisations as it expands. Every day explosive new developments and information swamp the health world and in order to keep on top of it we, as limited humans, have no other choice but to create specialties and allow members of our race to immerse themselves in a chosen area to such a depth that sometimes the most fundamental training of other areas becomes forgotten and lost.

Indeed, specialisation in the practice of medicine is not a modern production. The Egyptians subdivided their medical procedures to an absurd degree. In the Roman era, we read about the Syrian writer Lucian travelling all the way to Rome to consult an opthamologist. In Britain, medicine and surgery have been specialties for a thousand years. At the end of the 12th century Pope Innocent III considered the practice of surgery to be derogatory to the dignity of the priests (who were the principle medical practitioners at the time) and forbade them from carrying out surgeries. The priests did not want to relinquish a practice so lucrative and compromised by teaching surgical procedures to their barbers. Therefore, the surgeons of that day were operating technicians who took their instructions from physicians. One must wonder could this day ever reappear? The barbers however, eventually organised themselves into a guild which formed the beginning of the College of Surgeons and the division between medicine and surgery was born.

Although specialisation of sorts had its origins in days long past, the trained and recognised specialisations in medicine as we know them today had their chief growth during the last century. Medical activities have been subdivided to such an extent that we now have individuals whose sole focus is the function of one gland and others whose sole thought is for the symmetry of a single orifice. Even the general practitioners, I am sure, will admit that there is no single individual actually attempting to handle every type of case and that they themselves in some ways are becoming specialists.

There is no doubt that specialisation is inevitable and will increase. The recent additions to medical knowledge have made it utterly impossible for any individual to absorb more than a portion of it and practioners specialise, not essentially for materialistic reasons but because they realise the utter futility of attempting omniscience. Specialisation is imperative if work is to be done properly and if progress is to continue. In fact, modern specialisation represents the greatest general development medicine has ever known; it is merely a manifestation of the universal law of evolution witnessed in every biological process and every human activity - development from the simple to the complex, from the homogenous to the highly differentiated.

The TSMJ embraces this diversity. The journal gives trainee and newly qualified health science professionals, a chance to showcase their efforts and talents in their areas of interest. It provides both a hotbed to cultivate talent and an avenue of expression that it is an important learning source for those wishing to become involved with the research world.

Dr John O'Brien, an established generalist, opens the ninth edition with an interesting overview of the rural general practitioner of yore and modern times. His experiences in medicine are complimented later with an interview from Professor John Reynolds, a specialist surgeon.

The original research section contains three articles from very different aspects of the health scientists. Articles on the effect of continuous airway pressure on ventricular repolarisation in patients with heart failure and sleep apnoea, the impact of substance abuse in schizophrenia and a look into the provision of dental care for special care patients are included in this issue. Case studies on malrotation of the gut, extra-adrenal phaeochromocytoma and Crohn's disease in children teach us about some of the varied and remarkable surgical and medical cases encountered by practitioners on a daily basis. The review section also contains a variety of articles dealing with many different aspects of medicine including age related macular degeneration, Mohs micrographic surgery, vitamin B12 deficiency, modern methods in maxillofacial surgery and a novel connection between breast cancer and polymorphisms in previously unrelated genes. Medicine is a global phenomenon and we conclude this issue with sections composed of an article considering the influence of the law on the availability of medicines in developing countries and an elective experience in Malawi from where the author had a bird's eye view on the impact of poverty on health.

Finally, I would like to conclude by thanking all those who submitted to the TSMJ, whether it resulted in a publication or not, and appeal to students and health science professionals to regularly submit articles, on topics such as W.M.D.s of this issue, either to the TSMJ or other scientific journals. It is an important part of the health science world that is often over looked and sometimes under appreciated and so to quote one of the greatest journalists of all time William Allen White "dip your pen into your arteries and write".

James O'Byrne

Onward Rural Practice

Dr John O'Brien

The rural general practitioner (GP) of yore has been portrayed as a well educated wise gentleman, dressed in tweeds and wearing a bowtie. He reputedly feasted on the finest roast beef and relished his poached salmon. His night cap was a locally produced brew that arrived in a bag of potatoes at Christmas time. It was well known locally that he would not available when the Mayfly rose and was not to be disturbed when the shooting season commenced in November. His consultation fees were determined by his success on the stock exchange. He was reputed for his diagnostic skills, occasionally from the foot of the bed and this diagnosis would be eventually added to the local folklore. He often appeared on house calls dressed in his riding gear and night calls in his dress suit, probably coming from the local hunt ball or hospital dinner dance. On a wet night a family member would greet him at the entrance gate with the largest umbrella available to protect himself and his bag of medicines from the inclement weather.

He was a father figure locally, forming an indispensable part of the rural village trio of the priest, the doctor and the school teacher. He counselled families, wrote references for the children going to college, the bank or priesthood. He advised many young people emigrating to the United States or Great Britain. He offered sound advice on the Grand National, Cheltenham or the Derby and even upcoming shares but alas how things have changed. Today we are expected to be in our surgeries at the appointed time. Our diagnosis must be accurate, our treatment must be in keeping with the best international standards, our investigations must be appropriate and our referrals prompt. This is a far cry from the days of yore but Irish General Practice has always embraced change and will continue to embrace change that will benefit all our patients.

On appointment to a practice thirty years ago a doctor would arrive in a local village or town, where suitable accommodation would be scarce. The local dispensary would be run down, leaking and cold. This was also a time when the public and private patient did not sit comfortably together. Many garages and bicycle sheds were converted into waiting rooms and surgeries. The family sitting room often became a waiting room with much inconvenience to other family members. The good wife became secretary, receptionist, counsellor and door person. The rotas were onerous or non-existent with the doctor being available twenty four hours a day for three hundred and sixty-five days a year. A night at the theatre or at the local restaurant or an evening at the races was only possible if cover was provided by a neighbouring practitioner. For many rural practitioners there was a great sense of isolation. To my mind one of the greatest developments for GPs in this country was the formation of the Irish College of General Practitioners in 1984. This college was a unifying force for GPs, setting the education and standards for general practice. The continuous medical education, clinical society meetings and other education meetings under the auspices

Dr John O'Brien graduated from NUI Galway in 1973 and has worked as a GP in Doon, Co. Limerick since 1984. He is a member of the ICGP and RCGP, London and a tutor for Trinity College.

of the Irish College of General Practitioners created new meeting places for doctors and especially for the rural GP. These meetings are run by GPs for GPs but they are also a forum where doctors can seek the opinion of colleagues regarding diagnostic, managerial and ethical problems within the practice. The next milestone was the introduction of indicative drug budgeting and the Celtic Tiger in the nineties. GPs could now afford to develop new surgeries and many new health centres mushroomed around the country. Ancillary staff became part of rural practice. Computers were introduced to the rural practices creating links with the local hospital and allowing access to online journals and medical websites. Telephone conferencing became a possibility and a whole new era of communication was heralded in.

While we continue to carry out the normal routine of general practice every day, we also over the years have developed special clinics such as ante-natal, vaccinations, cervical screening, diabetic, heart watch, well man, well woman and minor surgery. Of course suturing is often performed in rural practice especially after a local hurling challenge. As many practices are quite a distance from the hospital we in the rural areas carry emergency equipment such as defibrillators, oxygen, intravenous infusions and intubating equipment. Some practitioners who are further away from hospital based services carry out thrombolysis in acute myocardial infarction.

Over the past ten years many towns and villages in rural Ireland have experienced a growth in population. This is due either to industrial development, influx of foreign nationals or where they have now become dormitory towns. Many places that were single handed practices will have to expand further to take extra doctors and extra personnel. The future doctor may well like his colleague of yore wear a bowtie if we are to follow the British direction however the rural practitioner may not be a gentleman but a lady because of the increased numbers of women entering the medical profession. The arrival of the primary care teams

will also involve GPs working together within a geographical area. These teams will include the local public health nurses, the community welfare officer, social worker and for the first time we will have the facilities of physiotherapists, occupational therapists, wound nurse, varicose vein nurse and speech therapists. In the future these primary care teams will be expanded to carry out ultrasound and perhaps x-ray examination and endoscopy. Today many of us receive our blood and x-ray reports online and in the future will see further integration of information technology into our practices.

As society changes new challenges will appear for the rural GP. Because of the increase in the population and especially an increase in the ageing population the workload for the general practitioner will increase. Also adding to this workload will be the increased incidences of diabetes mellitus, heart disease, obesity and hypertension. Addiction, once a problem of urban areas, is now extending to rural areas and practitioners will have to be educated on this problem. Continuous education has become increasingly important. The number of students in the medical colleges is on the increase and the colleges will be looking to GPs for increased numbers of training places in the future. Even part of the intern year may well take place within general practice. It will be imperative for the GP to keep abreast of all medical developments, to update his skills regularly and be a good teacher. Irish general practice has served its people well and the results of surveys have also been reassuring. This is part of the health service that works well and I wish that the people in charge would recognise that. We are independent contractors and we cherish that independence. To you students reading this article and especially to you who decide to enter general practice I would strongly urge you to hold on to that independence and never surrender it to any development group, department or executive.

It is a well recognised fact that in the presence of a well structured and organised primary care network, hospital services are used more appropriately, screening services are more efficient and in the long term this is beneficial to the economy. Irish general practice has changed dramatically in the past twenty-five years, especially in the rural areas with the introduction of co-operatives, purpose-built surgeries and ancillary staff. These developments have been of great benefit to doctors and patients alike. If we aim to maintain and improve standards and continue the momentum more support will be needed especially in the area of preventive medicine, education, teaching and research. I hope that rural practice will continue to be an intimate and caring form of medicine. As we look back we can be rightly proud of the service given by our predecessors. This noble profession can march forward with great hope, continue to embrace new changes and development, and hopefully will serve the local community well – so onward rural practice.

Winner of the Dean's Gold Medal

Improved Ventricular Repolarisation with Long-Term Continuous Positive Airway Pressure in Heart Failure Patients with Obstructive Sleep Apnoea: A Prospective Randomised Controlled Trial

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Clinical Points:

- Obstructive sleep apnoea (OSA) can coexist with heart failure, contributing to its harmful effects on heart function and the autonomic nervous system.
- Standard treatment for OSA is continuous positive airway pressure (CPAP), which creates a steady flow of air to keep the airway open preventing alveolar collapse.
- Temporal lability in ventricular repolarisation can be measured using beat-to-beat QT variability, referred to as the QT variability index (QTVI).
- Treatment of OSA by CPAP in patients with congestive heart failure improves left ventricular ejection fraction, overall sleep and reduces beat-to-beat QT variability, which may lead to a decrease in sudden cardiac death.

ABSTRACT

Background: Obstructive sleep apnoea (OSA) has a high prevalence in patients with congestive heart failure (CHF) and contributes to its progression. Periodic obstructive events subject the heart to recurrent episodes of nocturnal hypoxia and harmful effects on the autonomic nervous system, which can predispose the heart to ventricular arrhythmias. It has been shown that treatment with continuous positive airway pressure (CPAP) can improve cardiac and autonomic function in CHF patients with OSA. These improvements include increased left ventricular ejection fraction (LVEF), an increase in vagal tone, and a decrease in sympathetic drive. As autonomic tone, hypoxia, and afterload are known to modulate ventricular repolarisation (which is a determinant of malignant ventricular arrhythmias in heart failure patients), in this study we hypothesised that CPAP would improve ventricular repolarisation. The temporal lability of ventricular repolarisation can be measured using beat-to-beat QT variability (QTVI).

Methods: Eighteen patients with CHF (LVEF <45%) and OSA (apnoeas and hypopnoeas index (AHI) ≥20) underwent baseline polysomnography and echocardiography. QTVI was assessed from an electrocardiographic lead I during stage 2 sleep. The patients were then randomised to a control group (N=7, AHI=45.0 ± 15.0), or a CPAP treated group (N=11, AHI=40.2 ± 22.8) for one month, after which the above protocol was repeated.

Results: OSA was unchanged in the control group, but was alleviated in the CPAP group. The control group did not experience any significant changes in QTVI. In contrast, the CPAP treated group experienced a significant decrease in QTVI after one month (-0.37 ± 0.82 to -0.91 ± 0.55, P=0.006). This decrease in QTVI was significantly different between the two groups (P=0.021).

Conclusions: These findings indicate that in patients with CHF, treatment of coexisting OSA by CPAP improves ventricular repolarisation, which could reduce the risk of malignant arrhythmias.

INTRODUCTION

Congestive heart failure (CHF) affects over 80,000 people in Ireland with an annual incidence of 10,000 (1). It is estimated that with the aging population and high prevalence of coronary artery disease, that by the next decade as many as 300,000 Irish will be diagnosed with CHF (2). Despite advances in pharmacological treatments the rates of morbidity, hospitalisation, and mortality remain unacceptably high. Accordingly, it is important that secondary conditions that may contribute to the progression of CHF be identified and treated appropriately. In the last two decades a growing body of evidence indicates that one such condition, obstructive sleep apnoea (OSA), not only co-exists with heart failure (3,4), but also contributes to its harmful effects on heart function and the autonomic nervous system (5,6). Periodic obstructive events subject the heart to recurrent episodes of hypoxia, reduced vagal activity, surges in sympathetic nerve activity (SNA), heart rate (HR) and blood pressure (BP), and abnormal beat-to-beat changes in ventricular repolarisation (7-9). These nocturnal stresses are hazardous to the heart and have the potential to trigger ventricular arrhythmias (10). It is also well known that OSA triggers nocturnal

myocardial ischaemia (18), which could increase ventricular repolarisation lability (19,20). Abnormal ventricular repolarisation is also frequently seen in association with CHF (14-16) where it predisposes to the development of ventricular arrhythmias and sudden death (14,17).

The standard treatment for OSA is continuous positive airway pressure (CPAP), which effectively creates a steady flow of air to keep the airway open thereby preventing the collapse that leads to an apnoea. It is well known that CPAP decreases the apnoea/hypopnoea index (AHI) (apnoeas and hypopnoeas/hr of sleep) and improves overall sleep quality measured by polysomnography (11-13). The nocturnal stresses caused by OSA on the already failing heart can be acutely reversed by application of CPAP (11-13). CPAP has been shown to improve mechanical heart function (12), specifically by augmenting left ventricular ejection fraction (11,13). This is thought to be due to beneficial effects of dipping nocturnal blood pressure and decreasing sympathetic nerve activity (11,13). Despite these favourable improvements, the potential benefits of CPAP on ventricular arrhythmias are not yet established.
Temporal lability in ventricular repolarisation can be measured using beat-to-beat QT variability, referred to as the QT variability index (QTVI). Increased QTVI has been demonstrated in patients at risk of malignant ventricular arrhythmias including patients with dilated cardiomyopathy, unsuccessful reperfusion post-MI, and long QT syndrome (14,15). Because ventricular repolarisation can be modulated by autonomic tone, hypoxia, and afterload, we hypothesised that CPAP would not only improve LVEF, overall sleep, and abolish apnoeas, but would improve ventricular repolarisation as manifest by a decrease in QTVI. In the present study, we compared QTVI during stage 2 sleep in heart failure patients with OSA randomised to one month of CPAP versus no CPAP.

METHODS

Recruitment of Participants

Subjects were referred from the heart failure clinics at Mount Sinai Hospital and the Toronto General Hospital/University Health Network in Toronto for the investigation of possible sleep apnoea. Entry criteria consisted of: (i) CHF due to ischemic or non-ischaemic dilated cardiomyopathy, (ii) a resting left ventricular ejection fraction (LVEF) of 45% or less, (iii) stable functional capacity for at least one month prior to the study while on stable optimal heart failure medical management, (iv) the presence of OSA on a sleep study, defined as an AHI (apnoeas and hypopnoeas/hr of sleep) ≥ 20 and (v) a 5 minute continuous ECG recording at the end of the night during stage 2 sleep, devoid of apnoeas and hypopnoeas. Exclusion criteria were: (i) primary valvular heart disease, (ii) the presence of a cardiac pacemaker, (iii) atrial fibrillation, (iv) ventricular premature beats occurring at a rate greater than 5 per 100 heart beats (15) and (v) unstable angina, myocardial infarction, or cardiac surgery within 3 months of the study.

Assessment of Participants

The protocol was approved by the Human Subjects Review Committee of the University of Toronto and all subjects provided written informed consent prior to the study. Following a baseline sleep study and echocardiography, the subjects were randomly assigned to either a control group that were maintained on their optimal heart failure medical management (N=7), or a treatment group (N=11) that received CPAP in addition to their optimal heart failure medical management (see Table 1). The sleep study measured the AHI, oxyhaemoglobin saturation (SaO_2), arousals, heart rate, additional polysomnographic data (see Table 2), and QTVI analysis of the ECG tracing. The echocardiogram measured left ventricular function as LVEF upon waking. Subjects in the treatment group underwent an additional overnight sleep study during which CPAP was titrated to the pressure at which apnoeas and hypopnoeas were abolished, or to the highest tolerable pressure. They were then sent home with the CPAP device set at the optimum pressure and were instructed to apply it every night for at least six hours during the one month study period. The duration of CPAP usage was recorded via a built-in time metre to determine compliance.At the end of the one month study period, all patients underwent repeat sleep study and echocardiography to determine any changes in both the control and CPAP treated group. During the follow-up sleep study polysomnography was performed in the treatment group while on CPAP.

Sleep Studies

Sleep stages and arousals were scored according to standard criteria (21). Thoracoabdominal movements and airflow were measured by a calibrated respiratory inductance plethysmography (12). SaO_2 was monitored using an ear oximeter and HR via an electrocardiogram (ECG). Obstructive apnoeas were defined as tidal volume excursions of 0 to 100 ml for at least 10 seconds in the presence of out-of-phase movements of the ribcage and abdomen. Obstructive hypopnoeas were defined as 50% or greater reduction in tidal volume but above 100 ml for at least 10 seconds with out-of-phase ribcage and abdominal motion (12). Both these measures were used to calculate the AHI.

QT Variability Analysis

ECG recordings were taken from lead I over a continuous 5 minute period during stage 2 sleep when breathing was regular at the end of the night. ECG signals were sampled at 1000 Hz. The 5 minute epochs were analysed using a validated QT interval measurement algorithm programmed in MATLAB (Mathworks). Details of the algorithm operation are published extensively elsewhere (15). To measure beat-to-beat QT variability, a normalised QTVI, was derived according to the equation: log10[(QT variance / QT mean2) ÷ (heart rate variance / heart rate mean2)].

Power spectra of the heart rate (Pxx(f)) and QT (Pyy(f)) time series and the cross spectrum between the two (Pxy(f)) were computed from each epoch using the Blackman-Tukey method. The coherence was calculated using [Pxy(f)]^2 / [Pxx(f) Pyy(f)]. The coherence is a

measure from 0-1 of the degree of linear interaction between heart rate and QT fluctuations. Mean coherence was obtained by averaging the coherence over the frequency band from 0-0.2 Hz.

Left Ventricular Ejection Fraction Assessment

Two hours after the patient awakened, two-dimensional echocardiographic images were acquired from the parasternal long and short axes, apical long axis, apical four-chamber, and subcostal views by an echocardiographer who was unaware of the patient's treatment assignment. The LV end-diastolic and end-systolic dimensions were determined, and the LVEF was calculated according to a modification of Simpson's method (22).

Statistical Analysis

The data are expressed as mean ± standard devistion (SD) unless otherwise stated. A paired t-test was used to evaluate within-group differences while an unpaired t-test was used for between-group differences. Two-way repeated measures ANOVA tests were used to evaluate the time-treatment interactions within and between the groups at baseline and one month later. Non-normally distributed data were compared by the Mann-Whitney test. A P-value less than 0.05 was considered statistically significant. The statistical software package used was Sigmastat 2.03 (SPSS Inc.).

	Control group (N=7)	CPAP treated group (N=11)
Age, yr	57.1± 10.4	57.1± 7.8
Sex, M:F	6 : 1	9 : 2
Body mass index	31.3 ± 5.1	28.8 ± 6.1
Epworth Sleepiness Scale score †	5.1 ± 3.1	7.3 ± 3.5
Aetiology – no. of patients		
Ischaemic dilated cardiomyopathy	3	5
Non - ischemic dilated cardiomyopathy	4	6
NYHA class	2.4 ± 0.5	2.4 ± 0.7
LVEF %	27.7 ± 8.4	29.9 ± 13.4

Table 1. Baseline characteristics of the control and the CPAP treated groups. There were no significant differences between the two groups for any of the variables.
† The Epworth Sleepiness Scale ranges from 0 to 24, with scores of 10 or higher indicating excessive daytime sleepiness.
Abbreviations: NYHA = New York Heart Association, LVEF = left ventricular ejection fraction. Values are means ± SD.

RESULTS

Baseline Characteristics of the Subjects

Thirty subjects were enrolled in this study. Thirteen patients were randomly assigned to the control group and seventeen to the treatment group. Four subjects in the control group and three in the CPAP treatment group with ventricular premature beat rates of greater than 5% were excluded from further analysis. Two subjects in the control group and three subjects in the CPAP group were excluded from further analysis because of significant background noise in the ECG signal, making accurate identification of the QRS and T waves for QT analysis unreliable.

There were no significant baseline differences between the two groups with respect to age, gender, body-mass index (BMI), Epworth Sleepiness Scale scores, prevalence of ischemic and non-ischaemic cardiomyopathy, New York Heart Association functional class, or LVEF (see Table 1). Within the CPAP treated group the average compliance over the one month intervention period was 6.3 ± 1.5 hours per night with a minimum of 3.4 hrs/night and a maximum of 8.9 hrs/night. The average CPAP applied was 8.4 ± 2.4 cm H_2O.

Sleep Study Findings

There were no significant differences in AHI, sleep stage distribution, sleep efficiency, sleep time, average and lowest SaO_2, and arousals between the two groups at baseline. From baseline to follow up the control group experienced no significant changes in BMI, AHI, sleep stage distribution, sleep efficiency, sleep time, average and lowest SaO_2, or frequency of arousals. The CPAP treated group also had no significant changes in BMI, sleep efficiency, and sleep time during the one month treatment period. However, the CPAP group did experience significant decreases in AHI, frequency of arousals, and combined stage 1 and 2 sleep (p=0.003, p=0.007 and p=0.043 respectively). The decrease in AHI and frequency of arousals in the CPAP treated group were significantly greater than in controls (p=0.031 and p=0.038 respectively). The CPAP treated group also experienced significant increases in the average and lowest SaO2 throughout the night (p=0.015 and p=0.002 respectively) that were significantly greater than the control group (p=0.019 and p=0.008 respectively) (see Table 2).

Left Ventricular Ejection Fraction

After the one month follow up period, there was no significant change in LVEF in the control group (27.7 ± 8.4 to 30.7 ± 9.1%, p=0.38). However, the CPAP group experienced a statistically significant increase in LVEF after one month (29.9 ± 13.4 to 37.4 ± 12.6%, p=0.002) (data not shown).

QT Variability Results

There was no significant difference in the QTVI at baseline between the control and CPAP treated group (-0.77 ± 0.83 and –0.37 ± 0.82, respectively). In the control group, there was no significant difference in QTVI from baseline to follow up (-0.77 ± 0.83 to –0.56 ± 0.73). In the CPAP treated group there was a significant reduction in the QTVI from baseline to one month (-0.37 ± 0.82 to –0.91 ± 0.55, p=0.006) that was statistically significant when compared with the control group (p=0.021) (see Fig. 1).

	Control group(N=7)			CPAP treated group(N=11)		
	Baseline	1 mo	P-value	Baseline	1 mo	P-value
Body mass index	31.3 ± 5.1	31.7 ± 5.2	NS	28.8 ± 6.1	29.4 ± 6.1	NS
AHI (no/hr sleep)	45.0 ± 15.0	38.1 ± 15.3	NS	40.2 ± 22.8	6.0 ± 3.2	<0.001 ‡
Average SaO_2 (%)	94.5 ± 2.0	94.2 ± 1.9	NS	94.5 ± 1.5	95.9 ± 1.5	0.015 *
Lowest SaO_2 (%)	82.6 ± 7.0	78.8 ± 13.1	NS	81.8 ± 4.8	90.4 ± 3.5	<0.001 ||
TST (min)	288.4 ± 41.6	318.7 ± 47.3	NS	302.2 ± 74.3	325.3 ± 87.8	NS
Sleep Efficiency (%)	68.6 ± 10.8	74.0 ± 12.4	NS	68.2 ± 17.6	74.4 ± 17.3	NS
Stage I and II sleep (% of TST)	81.4 ± 7.1	78.6 ± 14.7	NS	83.9 ± 13.0	73.9 ± 14.0	0.043
Stage III and IV sleep (% of TST)	4.8 ± 5.2	5.2 ± 6.9	NS	8.0 ± 9.3	11.8 ± 12.1	NS
REM sleep (% of total sleep time)	13.9 ± 7.5	16.2 ± 9.4	NS	8.2 ± 5.7	14.2 ± 9.0	NS
Arousals (no/hr sleep)	42.8 ± 17.8	38.3 ± 11.6	NS	33.0 ± 21.9	11.7 ± 6.7	0.002 #

Table 2. Anthropomorphic and polysomnographic data.
Abbreviations: NS = not significant, AHI = apnoea/hypopnoea index, SaO2 = arterial oxyhaemoglobin saturation, TST = total sleep time and REM = rapid eye movement. Values are means ± SD. There were no significant differences in baseline values between the control and CP treated groups.
P-values refer to comparisons of within-group baseline to one month values.
‡ P=0.006 compared to the control group
* P=0.019 compared to the control group
|| P=0.003 compared to the control group
P=0.04 compared to the control group

DISCUSSION

By measuring QTVI in a randomised group of patients with CHF and OSA we were able to determine the effects of one month of CPAP usage on the temporal lability of ventricular repolarisation. The main finding of this prospective randomized controlled trial, was that nocturnal CPAP therapy for one month significantly decreased beat-to-beat QT variability in patients with CHF and OSA, in conjunction with alleviating OSA. Our findings are the first to suggest that long-term CPAP therapy improves ventricular repolarisation lability which may decrease the risk of ventricular arrhythmias in patients with OSA and existing heart failure.

We speculate that there are at least two mechanisms by which CPAP reduces beat-to-beat QT variability. Firstly, it is well known that myocardial ischaemia can influence ventricular repolarisation through a variety of mechanisms, including acidosis, and elevated extracellular potassium, which can change the duration and shape of the ventricular action potential (20, 23). It has been shown that QTVI increased markedly during ischaemic episodes in patients with coronary artery disease (19). Franklin et al have demonstrated that OSA can trigger nocturnal myocardial ischemia in patients with coronary artery disease (18). Alleviation of OSA and apnoea related hypoxia caused reversal of myocardial ischaemia in these patients. Therefore, the reversal of intermittent nocturnal hypoxia with CPAP, as observed in our study, may have contributed to the reduction in QTVI. Secondly, beat-to-beat QT variability may be influenced by changes in sympathetic and vagal tone (15,17,24,25). Evidence for this autonomic modulation came from a study by Yeragani et al., in which QT variability was found to increase significantly in normal adults after sympathetic stimulation, such as a head tilt test (24). A similar increase in QT variability was also found by Piccirillo et al. in CHF patients (25). Since, application of CPAP to patients with CHF and/or OSA decreases sympathetic nerve activity (26-29) and increases vagal modulation of HR (30-32), accordingly, an improvement in autonomic cardiovascular regulation with CPAP may reduce beat-to-beat QT variability. Additionally, it was found that, along with an abolishment of apnoeas and an improvement in sleep, there was an increase in LVEF. This restitution, which has been shown to be due to a decrease in sympathetic nerve activity (11), further illustrates augmentation of overall cardiac function.

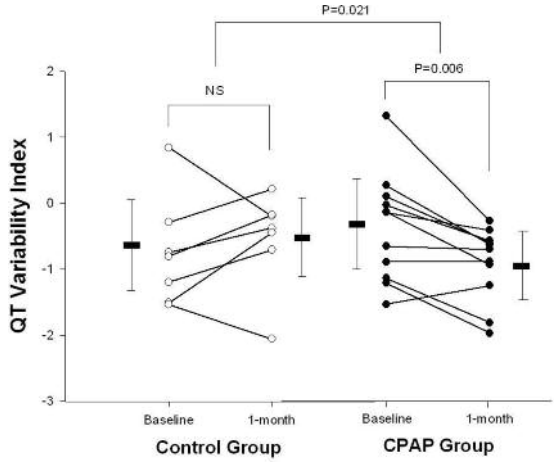

Fig. 1. A comparison of QT variability index (QTVI) in the continuous positive airway pressure (CPAP) and control groups at baseline and one month follow-up. In the control group there was no significant (NS) change in the QTVI from baseline to one month (-0.77 ± 0.83 to –0.56 ± 0.73). In contrast, there was a significant decrease in QTVI in the CPAP treated group (-0.37 ± 0.82 to –0.91 ± 0.55).
○ and ● are individual data for control and CPAP group respectively and □ are means ±SD.

CONCLUSIONS

Long-term treatment of OSA by CPAP in patients with CHF improves LVEF, overall sleep, and reduces beat-to-beat QT variability. Although the mechanism is unknown, the abolition of apnoea related hypoxia with CPAP may serve to reduce myocardial ischemia and improve ventricular repolarisation lability. Furthermore, a decrease in sympathetic nerve activity and/or increases in vagal tone may also play a significant role. Because increased beat-to-beat QT variability identifies patients at higher risk of sudden cardiac death (14), the effect of CPAP in CHF patients with OSA on ventricular arrhythmias merits further study.

ACKNOWLEDGEMENTS

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The Clinical Impact of Substance Use in Schizophrenia: A Study in an Irish Population.

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Clinical Points:

- Substance use is common among people with schizophrenia. 48% of participants in this study reported a history of substance use and/or alcohol misuse.
- Cannabis and alcohol were the most commonly used substances among schizophrenics.
- This study found no difference in the symptom profile between substance users and non-users.
- Cannabis use is associated with an earlier age at onset of illness and has an association to schizophrenia which is stronger than that of other substances. Cannabis use may, therefore, be a risk factor for the onset of schizophrenia.

ABSTRACT

Background: Substance use may be a risk factor for the onset of schizophrenia. However to date the impact of substance use in schizophrenia has not been fully explored in an Irish population. In this study we examine the clinical impact of substance use in schizophrenia within an Irish population.

Methods: The study sample consisted of 159 participants with a diagnosis of schizophrenia who were recruited to the ongoing Resource for Psychoses Genomics Ireland Study. All participants were interviewed with the Structured Clinical Interview for Diagnostic Statistical Manual IV to confirm diagnosis. Information on age at onset, illness course and substance use was collected at this interview and from case note review.

Results: In total, 48% of the participants reported lifetime substance use (including alcohol misuse). Cannabis was the most commonly used substance (82% of all users). Cannabis had an independent effect on the age at onset of psychosis, after adjusting for gender and use of substances other than cannabis. There was a trend towards more positive psychotic symptoms in substance users but it was not statistically significant.

Conclusions: Our results confirm the high lifetime prevalence of substance use in schizophrenia. In addition, results show an earlier age at onset of illness in cannabis users. This provides further evidence for the association between cannabis use and onset of schizophrenia, although causality cannot be assumed.

INTRODUCTION

Substance use in people with schizophrenia is up to five times more common than in the general population and is associated with a poorer clinical outcome (1,2). Substance use has also been implicated as a risk factor for the onset of schizophrenia (3). In a 2006 meta-analysis Talamo et al. showed that those with co-morbid substance use in schizophrenia have greater severity of positive symptoms and fewer "negative" symptoms than those without substance use (4). Previous studies in an urban, Irish population have estimated the prevalence of substance use among in-patients with schizophrenia and assessed its influence on depressive symptoms and suicidal ideation (5).

The aims of this study are to: 1) assess the lifetime prevalence of substance use among people with schizophrenia, 2) examine the association between substance use and the age at onset of schizophrenia, 3) examine the relationship between substance use and the severity of positive and "negative" symptoms of schizophrenia and 4) assess the association between substance use and global severity of illness.

METHODS

Recruitment of Participants

Participants were recruited to the ongoing Resource for Psychoses Genomics Ireland (RPGI) study. RPGI is a collaborative study between Trinity College Dublin; National University of Ireland, Dublin; National University of Ireland, Cork; Queen's University, Belfast; and The Royal College of Surgeons, Ireland. Participants were recruited through psychiatric services in the region of each university's research team, through lay support organisations and through self-referral from information provided in local and national media. The RPGI inclusion criteria required that participants i) be over 16 years of age, ii) have Irish born grandparents, iii) have a Diagnostic Statistical Manual IV (DSM-IV) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or bipolar affective disorder with psychosis and iv) be able to provide written informed consent. The RPGI exclusion criteria required that participants not have i) a substance-induced psychosis or medical disorder responsible for their psychosis or, ii) have a learning disability. All participants were assessed using the Structured Clinical Interview for DSM-IV (SCID). Those participants with a diagnosis of schizophrenia and who were entered onto the centralised electronic database (BCClin) before the arbitrary cut-off date July 20th, 2007,

were included in this study. This was in order to facilitate timely data analysis.

Assessment of Participants

Basic demographic data were collected directly from participants and from their case notes. SCID was used to elicit information on lifetime substance use and age at onset of illness. Mental state was assessed using the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of "Negative Symptoms" (SANS) (6). Scores for three symptom-derived syndromes of schizophrenia were calculated for each participant by adding together the global sub-scale scores pertaining to each factor and dividing by the maximum possible score to give a value between 0 and 1 for each factor. The syndromes were categorised as follows: positive syndrome (SAPS hallucinations and delusions), disorganisation syndrome (SAPS bizarre behaviour and positive formal thought disorder) and negative syndrome (all SANS sub-scales). Global severity of illness was assessed using the Global Assessment of Functioning Scale (GAF) (7). The GAF is a numeric scale (0 to 100) which rates the combined social, occupational and psychological functioning of an adult.

Statistical Analysis

The data were analysed using the Statistical Package for the Social Sciences, version 14 for Windows. In a comparison of participants with and without a history of substance use, the t-test was employed for continuous data and the x^2 test was used for categorical data. Age at onset of psychosis was used as the outcome variable in a linear regression model, and potentially influential variables (relating to gender and substance use) were entered as independent variables.

RESULTS

The Prevalence of Substance Use Among People with Schizophrenia

Of the 159 participants with schizophrenia 16.4% of participants reported substance use within the month previous to the interview and 47.8% reported substance use at some point during their lifetime. This lifetime figure of substance use is similar to previous estimates in an Irish population (5). From a list of substances including alcohol, ectasy, cocaine and heroin, cannabis was the most commonly used drug (39%) while aerosols was the least commonly used drug (0.6%). The 159 participant sample was divided into two sub-groups, one group reporting a history of substance use (and/or alcohol misuse) (N=76), and another group made up of those with no such history (N=83). Thirty four percent of the group reporting a history of substance use (and/or alcohol misuse) had abused a substance in the month previous to the interview.

Poly-substance use was a significant characteristic in the user group. Fifty nine percent of all substance users did so in tandem with at least one other substance while 35.5% of users used three or more substances (see Fig. 1.). Two thirds of cannabis users also used at least one other substance (data not shown).

	Total sample (N=159)	Substance users (N=76)
Time period		
In previous month	16.4	34.2
Lifetime	47.8	100
Substance used		
Cannabis	39.0	81.6
Alcohol	21.4	44.7
Ecstasy	13.8	28.9
Cocaine	11.9	25.0
Lysergic acid diethylamide	11.3	23.7
Amphetamine	6.9	14.5
Mushrooms	5.7	11.8
Heroin	2.5	5.3
Benzodiazepines	1.3	2.6
Ketamine	1.3	2.6
Aerosols	0.6	1.3

Table 1. Characterisation of substance use in schizophrenia. This table summarises the different substances used by this population of people with schizophrenia. The use of each substance is expressed, both as a percentage of the total sample (N=159), and of the subgroup of substance users (N=76). values presented arein percentages

The Association Between Substance Use and the Age at Onset of Illness

The demographic characteristics and GAF scores of the participants with or without a history of substance use are shown in Table 2. A younger age at interview and a younger age at onset of illness were both associated with a history of substance use.

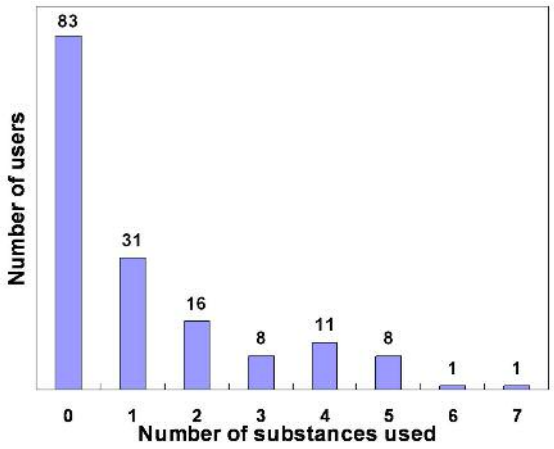

Fig. 1. Polysubstance use by a population of people with schizophrenia . This figure looks at the number of substances each of the 159 participants of this trial were using.

Characteristics	No lifetime history of substance use (N=83)	Any lifetime history of substance use (N=76)	Statistical Analysis t	x^2	p
Gender					
Male	61	84			
Female	39	16		9.16	0.002
Age at interview, years	45.9 ± 12.1	36.4 ± 11.7	-4.95		<0.001
Age at onset, years	25.0± 8.7	22.6 ± 7.6	-1.85		0.066
G.A.F. scores	58.0 ± 18.4	62.2 ± 13.9	1.59		0.114

Table 2. Clinical characteristics of people with schizophrenia, both with and without a lifetime history of substance use. This table summarises certain characteristics such as gender, age at interview, age at onset of illness, and G.A.F scores that existed in the two groups; i.e. those with any lifetime history of substance use and those with no lifetime history of substance use. The mean ± SD values are given for age, age at onset and G.A.F while the gender is expressed as a percentage.

	Mean difference in age at onset of illness (years)	Confidence intervals (years)		p
Female	-2.1	-0.81	- 3.4	0.156
Use of substances other than cannabis	+3.9	-0.63	- 7.2	0.091
Cannabis use	-4.3	-2.0	- 6.7	0.001

Table 3. Mean age difference at onset of illness by gender, non-cannabis-drug-use, and cannabis use. Gender, non-cannabis-drug-use, and cannabis use were entered as independent variables in a linear regression analysis, with age at onset of illness as the outcome variable. Only cannabis use proved significant after the variances of the other independent variables were controlled for.

Linear regression analysis was performed with age at onset of illness as the outcome variable and the following independent variables: gender, cannabis use and use of substances other than cannabis (see Table 3.). When the variances of all the independent variables were controlled for, the use of substances other than cannabis and gender were not significant in relation to age at onset of illness. Cannabis use was significantly associated with a younger age at onset of illness after adjusting for gender and substance use other than cannabis. A comparison of the means revealed that cannabis users had a younger age at onset of illness by a mean value of 4.3 years (95% CI 2.0 to 6.7, p<0.001) (see Table 3).

The Association Between Substance Use and the Type of Symptoms

The clinical assessments that were administered to the participants with and without a history of substance use are summarised in Table 4. No significant differences were found between the two groups with regard to positive and "negative" syndromes. A separate analysis comparing those with a history of cannabis use to those without revealed that those who reported cannabis use experienced more types of positive symptoms than those who did not (mean difference 1.7, t=3.5, p=0.001).

The Relationship of Substance Use with Global Severity of Illness

GAF scores are listed in Table 2. No significant difference was found between those with a history of substance use and those without such a history.

DISCUSSION

The association between substance use and schizophrenia is well documented (1,2). The aims of this study were to assess the association between substance use and the nature and severity of symptoms in schizophrenia, the age at onset of illness and the global severity of illness in an Irish population.

A significant result in this study was that a younger age at onset of psychosis was found in those participants who had reported a history of substance use. The most commonly used drug was cannabis. Participants with a history of cannabis use had a significantly younger age at onset after controlling for other possible confounding factors. This means that those participants with a history of cannabis use had an earlier age at onset of psychosis than other participants who had not used cannabis but who shared the same profile with regard to the other variables. A possible explanation for this pattern is that substance use precipitates the illness, although it remains unclear whether or not this effect is confined to those with a predisposition to psychosis (8). Another possible explanation could be that the symptoms of schizophrenia lead to a tendency towards substance use (9).

Previous studies have addressed the temporal relationship between substance use and onset of psychosis but not the relationship between substance use and the schizophrenia prodrome (10). The data did not allow us to determine whether or not the substance use preceded the onset of illness. Also, the amount of multiple-substance-use limited the analysis of the unique contribution of any particular substance. However, the results of the linear regression analysis suggest that cannabis is more closely linked with

Syndromes assessed	No lifetime history of substance use (N=83)		Any lifetime history of substance use (N=76)		t	p
Positive syndrome:	0.41	± 0.26	0.44	± 0.26	0.59	0.56
Disorganisation syndrome:	0.36	± 0.17	0.31	± 0.15	-1.94	0.054
Negative syndrome:	0.56	± 0.22	0.53	± 0.18	-0.1	0.32
Total variety of lifetime positive symptoms (number of different symptoms)	5.16	± 3.53	6.51	± 2.97	2.61	0.01

Table 4. Clinical assessments for participants with and without a history of substance use. This table summarises the difference in syndrome scores between the two groups. The three syndromes were: positive syndrome, disorganisation syndrome and negative syndrome. The total variety of lifetime positive symptoms is also presented for both groups. The syndromes were measured using the symptom-based syndrome score (0-1). The mean ± SD are given for each score.

earlier onset of illness than other drugs. This finding is in line with the results of other studies (11).

There were no significant differences in symptom scores between substance users and non-users. This correlates with a previous study in an Irish population which did not find an association between substance use and depressive symptoms (5). It has been reported elsewhere that substance use is associated with more positive symptoms (12). A weakness of this study is that the positive symptoms were only graded for their severity during the previous month, and not over the duration of the illness. However, the total variety of lifetime positive symptoms was increased in substance users, with cannabis users in particular experiencing almost two more types of symptom than non cannabis-users.

No association was found between global rating of functioning and substance use. It has been reported elsewhere that people with schizophrenia and co-morbid substance use have a more severe form of illness (4).

CONCLUSIONS

In conclusion this study demonstrates the earlier age at onset of illness in substance users and in cannabis users in particular. The results confirm the high lifetime prevalence of substance use in schizophrenia. Although cannabis and alcohol were the most commonly used substances, most of the participants reported using multiple substances. Substance use tends to predict a poorer clinical outcome and therefore it is important to ask patients about their substance use and consider appropriate psychosocial intervention in people with schizophrenia. Also, clinicians should advocate abstinence from substance use (including cannabis) as it may be a risk factor for the onset of schizophrenia.

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Provision of Dental Care for Special Care Patients in Ireland: A Qualitative and Quantitative Study

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Clinical Points:

- Approximately two-thirds of general dental practicioners in Ireland are currently treating special care patients.
- 26% of respondents have an awareness of the implications of the Disability Act 2005 for their practice.
- Emergency services are the most frequent treatment provided for Special Care Patients.
- Those who treat Special Care Patients are less likely to feel that additional fees are required.
- Behaviour and communication difficulties are the most frequently cited barrier to care.

ABSTRACT:
Background: Special care dentistry (SCD) is becoming an important part of dentistry in Ireland. The aim of the study is to assess the provision of dental services for special care patients (SCP) by general dental practitioners (GDP) in Ireland and to evaluate the previous training background and determine the type of additional education or training required by GDPs.
Methods: A postal and on-line questionnaire was sent to every third member of the Dental Register in Ireland. An analysis of the data was performed using the Statistical Programme for Social Sciences.
Results: The response rate to the questionnaire was 35%. The reported level of GDPs with previous training in SCD was 42%, the level expressing a willingness to partake in further training was 62%. Emergency treatments were the most commonly provided service (70%), this was followed by extractions (67%) and restorative treatment (67%). Oral Hygiene Instruction for the carers of SCP was provided by 49% of respondents. An awareness of Disability Act was reported by 26%. Analysis of both the definitions of SCD and the barriers to dental care showed a variety of responses. Additional fees for the treatment of SCP were deemed necessary by 65% of respondents.
Conclusions: Whilst the treatment of SCP was reported by the majority of respondents this included primarily emergency services. The need for a greater focus on prevention was highlighted, as was the requirement for improved training of dental practitioners in SCD. Knowledge of the 2005 Disability Act was limited and thus further promotion of its implications for the profession is indicated.

INTRODUCTION

The field of Special Care Dentistry (SCD) has gained increasing recognition in Ireland in recent years. With regard to the International Classification of Functioning, Disability and Health, efforts to classify this patient group propose that "persons requiring special care dentistry are those with a disability or activity restriction that directly or indirectly affects their oral health, within the personal and environmental context of the individual" (1). In Ireland the development of a National Disability Act in 2005 (2), which looks to promote equality and social inclusion, defines disability as "a substantial restriction in the capacity of the person to carry on a profession, business or occupation in the State or to participate in social or cultural life in the State by reason of and enduring physical, sensory, mental health or intellectual impairment." Access to dental services for such individuals comes under the remit of this act.

The inequalities in oral health and care services have been identified through national oral health surveys of children and adolescents in Ireland during 2002 and 2003 (3), reporting a 30% increase in untreated dental decay in children with disabilities (3). The treatment of special care patients (SCP) presents general dental practitioners (GDPs) with various challenges which may ultimately become a barrier to the provision of care at its highest standard. In the United Kingdom a policy document was developed to aid practitioners in addressing these barriers, most notably regarding legal issues and physical interventions (4).

In Northern Ireland a comprehensive study of both people with learning disabilities and service providers (5) identified a higher level of oral disease with a concurrent low level of treatment provision and more extractions, than their peers in the general population. It also recognised the need for further training of dental practitioners and their staff, particularly at an undergraduate level (5). The need to improve training in both medical and dental disciplines has been recognised as a means to improve oral health services for these patients (6). This is evident with the formation of organisations such as the American Academy of Developmental Medicine and Dentistry (AADMD) (6).

Research looking at the provision of services from a patient's perspective has noted that experience of dental services was related to the attitude and skills of the dental health professionals, stigma, relatives' expectations of dentists, their oral health beliefs, information and support received, and knowledge and priorities. Relatives

expressed their desire for information provision in the general health setting (7).

This study aims to ascertain the provision and range of oral health services for SCP by GDPs in Ireland. It is also intended to establish any barriers that may exist to care in this country. As training has been identified as an essential adjunct to the improvement of care services (5,6,8), the background and type of additional education or training required will be evaluated.

METHODS

The study was approved by the Trinity College Dublin Faculty of Health Sciences Research Ethics Committee. The questionnaire was designed to include both quantitative and qualitative data. To develop the survey instrument, twenty clinical supervisors and house officers agreed to partake in a pilot study. Subsequent to this the responses were analysed for further development of the questionnaire. Study participants were selected from the Irish Dental Register 2007 and every third member with an address in Ireland was sent a self-completed questionnaire and given the option of an on-line alternative. In total 782 finalised questionnaires were posted and participants were asked to return them by the end of November 2007. One month following postage a reminder was published in the Irish Dental Association newsletter to encourage participation.

The questionnaire topics primarily assessed demographic factors (age and gender) and practice-related demographics (field of dental practice, dental school, practice location and distance from nearest dental hospital). Participants were then asked to define SCD, and history and opinions of training in SCD were assessed. Experience of the treatment of SCP, concerns, satisfactions and their opinion as to whether additional fees are required were then determined. The provision of oral health instruction for carers, knowledge of the Disability Act and accessibility to a trained dental nurse, hygienist and physical access to the practice were also evaluated. Further suggestions were welcomed at the conclusion of the survey.

The collected data were then entered into a Microsoft Excel document. An analysis of the data was performed using Statistical Programme for Social Science software.

RESULTS

Of the 782 dental practitioners who received the survey, 272 returned the paper-based survey and 2 responded via the on-line version; yielding a response rate of 35%. A total of 267 were analysed (34% of total) after exclusion of 7 questionnaires (retired/no longer at given address).

Respondents were predominantly GDPs (57%) and males over the age of 51 (21%). The reported proportion with previous training in SCD was 42% and of this; undergraduate training comprised 18%, postgraduate 12% and both undergraduate and postgraduate 12% of respondents. Of those surveyed, 12% reported having had hands on experience during training, a further 36% believed that hands-on experience is required in training and 62% expressed a willingness to train.

It was found that 65% of those surveyed are currently treating SCP (see Fig. 1). Treatments provided include: 70% emergency service, 67% extractions, 67% restorative treatments, 57% dental screening, 54% periodontal, 45% dentures, 12% sedation, 7% outreach screening programmes. Oral hygiene instruction (OHI) for the carers of SCP was provided by 49% of respondents and 26% of those surveyed claimed an awareness of Disability Act. Access to the practice was reported as inadequate in 44 % of the study group.

Barriers to care include behaviour and communication difficulties (22%), the treatment of SCP outside of practitioners remit/capabilities (18%), concern regarding medical history of SCP (18%), concerns with finance and time (16%), inadequate sedation/GA referral facilities (11%), physical access problems (8%), consent (6%), carer lack of knowledge (5%), treatment relapse (4%) and staffing issues (1%).

When asked to define SCD, 25% alluded to mental or physical disabilities only with 10% providing a more comprehensive answer. Practitioners were asked for their opinion regarding the requirement for additional fees in the treatment of SCP and interestingly almost half of those practitioners treating and not trating SCP agreed that additional fees are required (see Fig. 1.).

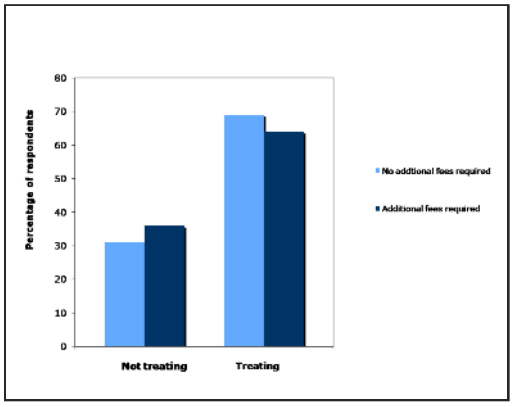

Fig. 1. Percentage of dentists who: i) do treat / do not treat SCP and ii) feel additional fees are required and not required for this patient group.
A postal questionnaire and an option of an online reply was given to sent to every third member of the Dental Register in Ireland. The figure compares the number of respondents who currently treat and do not treat SCP and also those who feel additional fees are required (navy) and those who do not feel additional fees are required for the treatment (light blue).

DISCUSSION AND CONCLUSION

This study reports the findings of a quantitative and qualitative survey of Irish dental practitioners and the provision of services for SCP. The results show a low level of previous training in SCD, yet a high level of interest to partake in further education in this field. A significant number of practitioners felt that hands-on experience was essential in the training process. This is encouraging as similar research has highlighted training and education as a means to improve service provision for this patient group (5,6,8).

The treatment of SCP was reported by approximately two-thirds of participants. Disappointingly the most commonly reported treatments included emergency services, extractions and restorative care, with the low level of OHI provision highlighted. At the heart of public health provision is prevention and never is this more relevant than with SCP where the high prevalence of poor oral health and the significant challenges that exist in the provision of treatment merit a strong focus on preventative strategies.

Interestingly a higher percentage of those with previous training in SCD report treatment of SCP and those who currently treat SCP do not feel that additional fees are required. A low level of knowledge regarding the law as it relates to provision of treatment for disabled persons emphasises the need of increase awareness of the Disability Act of 2005, thus increasing both provider and consumer knowledge of their rights and access to care. It must be noted however that due to the relatively low response rate these results are likely to be biased in favour of those with an interest in SCD.

A similar study targeting in particular Irish Health Board Dental Surgeons treating those with special needs was conducted in 2001 in order to assess the current dental health services for those categorised as special needs by the Department of Health and Children (DoHC). The study made a number of recommendations for the development of the service in Ireland, namely the development of explicit policies for the provision of care for special needs groups, the introduction of a Specialist Register and the establishment of training programs. It was advised that planning more appropriate preventive dental health programmes was necessary with expansion of those services where dental hygienists and oral health promoters, specifically for SCP are available. It was recognised that there is a need for the expansion of existing services for the treatment of SCP under general anaesthetic (9).

Based on the findings from the study the authors wish to make a number of their own recommendations. There is a need for enhanced training at an undergraduate level with an emphasis on clinical experience in a supervised environment. The level of interest in further training would suggest the requirement for dedicated special care dentistry postgraduate courses, in addition to modules in SCD within Continued Professional Development programmes. The impact and legalities of the Disability Act introduced in Ireland in 2005 should be promoted among the profession. Education programmes for the carers of SCP ought to be established, with the importance of the active practice of preventative dentistry highlighted. The active involvement of all members of the patients' medical team, i.e. the medical practitioners or specialists and the GDPs, allows for the provision of a multi-strategic, holistic approach addressing all aspects of health.

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Fifteen Minutes with a Surgeon

Professor John Vincent Reynolds

WHAT WAS YOUR ROUTE FROM MEDICAL SCHOOL TO YOUR PRESENT POSITION IN ANATOMY?

I completed my primary medical degree at University College Dublin in 1981 (MB. B.Ch. BAO). In 1985 I achieved my Fellowship at the Royal College of Surgeons of Ireland (FRCSI) and in 1990 I obtained my higher degree, a Masters of Surgery (MCh).

My time abroad was spent initially as a Research Fellow in the hospital of the University of Pennsylvania and the Wistar Institute, Philadelphia, between 1986 and 1988. In 1990, I was a lecturer at St. Mary's Hospital, London and Imperial College. Between 1993 and 1994 I took up an International clinical Fellowship in Surgical Oncology in the Memorial Sloan Kettering Cancer Centre, New York. I was Senior Lecturer at the University of Leeds before returning to Ireland.

IS MEDICINE IN YOUR FAMILY AND HAVE YOU ALWAYS WANTED TO BE A DOCTOR?

No, I am the only doctor in a large family, we have no shortage of lawyers. I didn't think deeply about careers when at school in Templeogue College, and would have been happy with any of the health sciences or law. I chose dentistry and did one year before switching to medicine.

WHY DID YOU DECIDE UPON SURGERY?

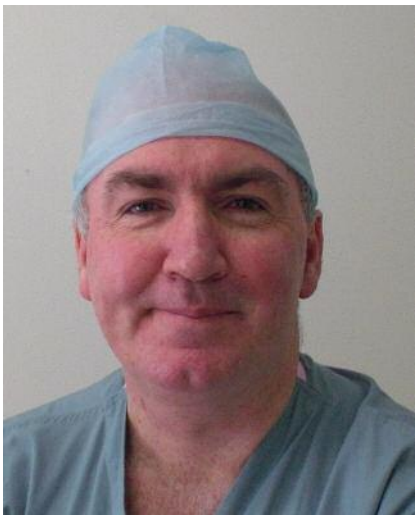
I decided upon a surgical career in my first clinical year in medicine at St.Vincent's Hospital. I enjoyed the dynamics and excitement of the operating room, the emergency room, and critical care settings. I have always been very interested in cancer, and may have been a medical oncologist if I had not chosen surgery. I would also have been very happy, I think, as an academic scientist, again most probably with a focus on cancer. As a professor of surgery, I have an opportunity to combine surgery, cancer, and cancer research, and am very content with this mix of the art and science of my discipline.

WHAT RESEARCH ARE YOU CURRENTLY INVOLVED IN?

I am currently involved in a number of projects including: assessing the role of antioxidants in inflammation to cancer pathway in the oesophagus; using genomics and proteomics to helps predict the response of cancer to preoperative chemotherapy and radiation therapy and studies of visceral adiposity and metabolic syndrome in cancer patients.

WHAT ARE YOUR FAVORITE SURGICAL OPERATIONS?

Thyroidectomy, oesophagectomy and Whipple resections are nice technical operations where precise anatomical sharp dissections are required.



Professor John Vincent Reynolds is Professor of Surgery in Trinity College Dublin since 2001. He is also Regional Director for Cancer Services in South-West Dublin, a Principal Investigator at Dublin Molecular Medicine Centre and Scientific Director of the Cancer Clinical Trials Consortium.

WHAT DO YOU DO IN YOUR FREE TIME?

During school and college days I was involved in a number of sports including soccer, rugby, gaelic games and tennis. Now I play lousy tennis and golf. I read a lot in my spare time, in particular history and science.

HAVE YOU HAD ANY REGRETS TO DATE?

I have no regrets in my career. I did, however, give up the piano in at the age of thirteen after eight years of lessons. I had completed all the grades up until then, but decided to devote all my time to getting signed by Liverpool F.C. - that was a mistake.

FINALLY HAVE YOU ANY ADVICE FOR JUNIOR DOCTORS AND MEDICAL STUDENTS?

It is difficult to give general advice as the career spectrum is so broad. This is one of the reasons why I switched early from dentistry. For anyone who truly loves the surgical environment as a student and is prepared to put in the hours, back yourself and stick with it. When weighed against the satisfaction and privilege of professional life that surgery affords, the career path is not as arduous as many students and young doctors imagine.

32-Year-Old Man with Abdominal Pain, General Malaise and an Inability to Eat: A Case of Intestinal Malrotation

Katie O' Sullivan
Sixth Year Medicine, TCD

Clinical Points:

- Intestinal malrotation can lead to volvulus (a twist of the gut around its mesenteric axis which compromises blood supply) in adults.
- Symptoms are bilious vomiting and acute bowel obstruction on a background of recurrent, crampy abdominal pain and episodes of nausea and vomiting.
- A high index of suspicion is crucial when a patient repeatedly presents with abdominal pain and an inability to eat as a malrotation of the intestine is a rare but serious condition.
- Management of the condition is surgical and traditionally comprises a Ladd's procedure with variations of the procedure depending on the intestinal anatomy involved.

PRESENTATION OF CASE

Mr. X, a 32-year-old Egyptian man, presented to the emergency department of a country hospital complaining of an eight day history of persistent abdominal pain, general malaise and inability to eat. There was epigastric pain that had an abrupt onset, was sharp in nature and radiated to the lower abdomen. It was associated with nausea, vomiting, constipation and was exacerbated by movement. He had no symptoms of urinary tract infection. Upon admission he experienced one episode of bile stained vomiting. His history revealed two previous presentations to the emergency department complaining of similar abdominal pain. On the first occasion eight days previously no diagnosis had been made. On the second occasion, three days previously, Mr. X was diagnosed with both grade one gastritis and duodenitis and was discharged on a course of triple therapy of full dose proton pump inhibitor omeprazole (20mg OD), amoxicillin (1g BD) and clarithromycin (250mg BD) for seven days. This failed to alleviate symptoms.

He had a positive family history of hypertension and diabetes. He was a non-smoker and non-drinker. On examination the patient was in acute pain, afebrile with a temperature of 37.6ºC. He was mildly tachycardic and hypertensive with a blood pressure of 152/112 mmHg. Other vital signs were normal. His abdomen was non-distended however there was guarding and tenderness in the epigastric and left upper quadrant region. Bowel sounds were present and hernial orifices were free.

INVESTIGATIONS AND DIAGNOSIS

On presentation three days previous to the current presentation, blood results had revealed haemoglobin, haematocrit, biochemistry, clotting and coeliac screens and thyroid function to be normal. C-reactive protein was at the upper limit of normal and alanine aminotransferase was slightly raised. Urine microscopy was unremarkable. Radiological investigations of the abdomen were carried out. A plain film of the abdomen was normal, and abdominal ultrasound confirmed the absence of gallstones and normal liver, biliary tree, spleen and kidneys. Gastric and duodenal biopsies taken during an oesophagogastroduodenoscopy (OGD) revealed grade one gastritis over the fundus, body and pylorus of stomach and grade one duodenitis. Campylobacter-like organism (Clo) testing was carried out and confirmed *Helicobacter pylori*. The patient at this time was commenced and discharged on triple therapy.

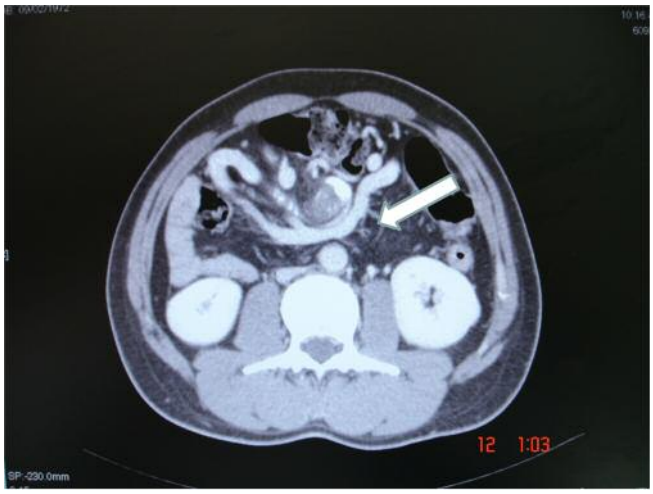


Fig. 1. A CT image of the abdomen of Mr X.
In this CT an arrow points to a whorled appearance of the small mesenteric artery and small mesenteric vein in the central upper abdomen consistent with volvulus. Also evidence of venous congestion of the mesentery exists.

On current presentation, follow through contrast studies of the small bowel revealed delayed passage of barium from the stomach, a midline duodenojejunal flexure, predominate localisation of the small bowel to the right upper abdomen and a high caecal pole. A diagnosis of malrotation was made. In contrast studies malrotation can appear as corkscrew tapering of the duodenum or jejunum. The 'corkscrew sign' is due to intestinal obstruction, but this is not always a reliable sign. Malrotation may also be diagnosed by computed tomography (CT). Abdominal CT was carried out and revealed a whorled appearance in the central abdomen extending below the origin of the superior mesenteric artery.

This so called “whirlpool sign’ describes the cross sectional appearances of the twisted mesenteric vessels (2, 3) and is pathognomic for the condition(see Fig. 1.). It is a well recognised clinical sign in neonates and can be seen in adults. This provides an immediate diagnosis of malrotation and allowing prompt action. Absence of a dilated bowel suggested that the volvulus was likely to be intermittent.

Diagnosis of intestinal malrotation on clinical grounds is difficult to make, as illustrated by the case of Mr X. Patients often have numerous medical consultations before a diagnosis is made (1). Therefore, a high index of suspicion is crucial when a patient repeatedly presents with the symptoms described in the case presentation. Another challenge that often presents is the presence of co-existing gastrointestinal complaints, also illustrated by the case of Mr X. When the presence of gastritis was confirmed on OGD, a seemingly plausible reason for his symptoms of abdominal pain was found. Malrotation can often mimic other gastro-intestinal diseases.

MANAGEMENT

Mr X was managed conservatively with analgesia for five days. A laparotomy with division of fibrous bands of tissue, Ladd’s bands, and a caecopexy were then performed. Operative findings confirmed a malrotation and revealed a narrow small mesentery, a wide band compressing the 2nd and 3rd parts of the duodenum and the presence of Meckel’s diverticulum (a persistence of the vitelline duct that occurs in 2-4% of people). The remaining abdominal contents were normal.

Management of malrotation relies on speed of diagnosis and prompt surgical correction. In an acute situation placement of a nasogastric tube, IV access and administration of parenteral antibiotics should be accomplished without delay (4). The traditional surgical procedure, the Ladd procedure consists of: i) envisceration of the bowel and inspection of the mesenteric root, ii) counter clockwise derotation of the volvulus, iii) lysis of Ladd’s bands with straightening of the duodenum, iv) an appendecectomy and v) placement of the cecum in the left lower quadrant. However, as illustrated by our case, there are acceptable variations of this procedure depending on the anatomical geography involved. There have been a number of small studies comparing the use of open and laparoscopic procedures, however, because of the absence of larger studies, no clear recommendations have been made regarding the best method of surgical treatment (5,6).

DISCUSSION

Intestinal malrotation is a congenital abnormality of the gastrointestinal tract that predisposes to duodenal obstruction and midgut volvulus and can lead to ischaemic necrosis of the small bowel if undiagnosed (7). It is a very rare presentation in adulthood (7,8) as 60% of cases are diagnosed within the first month of life, 20% between one month and a year and a further 20% are usually diagnosed before the end of childhood. There is a wide variation in reported incidence from 1:500 to 1:6,000 (9) with a male predominance of 2:1 (10).

During the foetal growth a variety of important time points exist for the development of the midgut. At the beginning of week six, rapid elongation of the midgut begins and liver growth reduces the abdominal cavity pushing the intestine into a cavity in the umbilical cord, a process called physiological umbilical herniation. As the loop continues to grow in length, it rotates around an axis formed by the superior mesenteric artery root. When viewed front-on, this happens in a counter clockwise direction and turns a total of 270º before then returning to the abdominal cavity (1). If the rotation is less than 270º, the mesentery may have a narrow base and allow the bowel to rotate on the superior mesenteric axis, creating a volvulus and compromising blood supply. At week ten, intestinal loops begin to return to the abdominal cavity. The factors involved are not entirely known, but abdominal expansion and a reduced rate of liver growth are thought to play a role. The proximal jejunum enters first and goes to the left of the abdominal cavity. This is followed by the remaining loops which settle to the right. The caecal bud is the last part to re-enter. At first it lies in the right upper quadrant but then descends into the right iliac fossa and therefore places the ascending colon and hepatic flexure on the right hand side of the abdominal cavity (11,12). A fusion process then adheres the gut to the posterior abdominal wall resulting in fixation of the colon in the retroperitoneal space. The fascial attachments involved in holding the right and left colon in place are called the fascial fusion planes of Toldt, while the ligament of Treitz fuses the duodenum to the retroperitoneum. It is these broad based attachments which usually limit the mobility of the gut and prevent volvulus and kinking of the vascular supply to the gut. Abdominal rotation and attachment are completed by end of the first trimester (13). If a disruption occurs in this rotation six types of malrotation are possible (14), the commonest involving failure of the caecum to move into the right lower quadrant (15). In addition, Ladd’s bands may cross and obstruct the duodenum (7).

All types of malrotation can lead to the development of a volvulus, a twist of the gut around its mesenteric axis. This occurs due to shortness of the mesenteric root (line of mesenteric fixation to the posterior wall of the abdominal cavity) and the narrowness of the resulting suspensory pedicle of the gut (3,10,16). It is the most feared complication of malrotation as it has a mortality rate of 18-25% if it remains undiagnosed (7,17,18,19).

ACKNOWLEDGEMENTS

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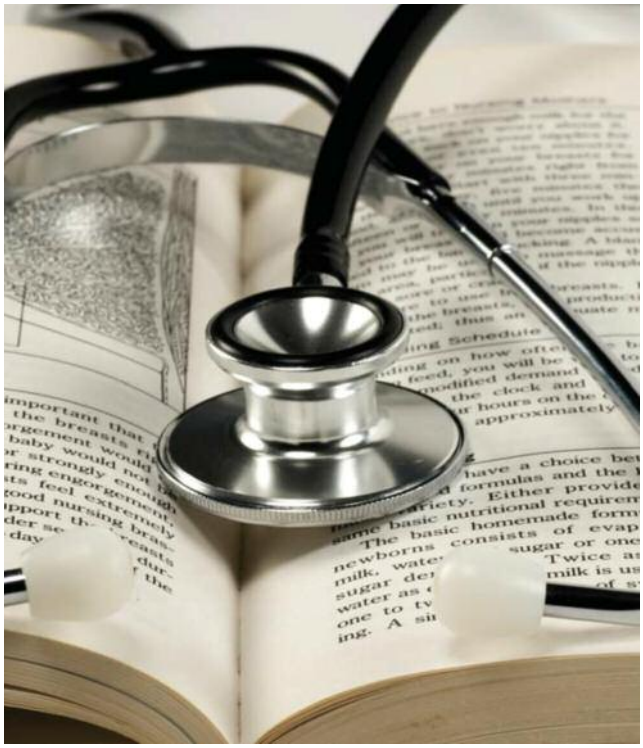

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41-Year-Old Man with Severe Headaches and Heart Palpitations: A Case of a Recurring, Extra-Adrenal Phaeochromocytoma

Nigel S. Rajaretnam

Sixth Year Medicine, TCD

Clinical Points:

- Extra adrenal phaeochromocytoma should be considered in the differential diagnosis for patients presenting with severe headaches and heart palpitations.
- Investigations that are used to diagnose a phaeochromocytoma include a 24 hour urine catecholamine collection, magnetic resonance imaging, computerised tomography and I^{131} metaiodobenzylguanidine scans.
- Surgery is the mainstay treatment, though some phaeochromocytomas may respond to radiotherapy or chemotherapy.
- An annual follow up is important in patients who are susceptible to recurring phaeochromocytomas.
- Phaeochromocytomas are tumours of the rule of 10 – 10% of tumours are malignant, 10% are extra adrenal 10% occur in children, 10% are bilateral and 10% are familial.

PRESENTATION OF CASE

Patient K, a 41 year old man, presented to a surgical outpatient clinic as a general practitioner (GP) referral because he was suffering from severe headaches and heart palpitations. The patient described the headache as a sharp pain that rated 9 on a scale of 0 -10 (with 10 representing the most severe pain) that encapsulated the whole of the cranium which was sometimes so severe that he would have to stop working and lie down to find relief. He reported that analgesia was not helpful and that physical exercise exacerbated the symptoms. At time of presentation the headaches occurred 2-3 times every day and varied in duration between 10 minutes to an hour. In addition, there were no associated visual disturbances, photophobia, phonophobia or aura. The patient also reported random heart palpitations, which would last 20-30 minutes occurring throughout the day even when lying down. They were not brought on by any single action and were not associated with any pain or shortness or breath, but they sometimes preceded a headache.

K had a background history of phaeochromocytoma for which a right adrenal mass was excised in his home country of Pakistan nine years previous to presentation. The headaches and heart palpitations had initially developed six years previous to the current presentation and since then K had presented to his GP eight times with the same complaint but with worsening severity. During this time, his blood pressure remained within normal limits and 24 hour blood pressure monitoring was also found to be normal. A computed tomography (CT) scan, carried out three years previous to the current presentation,

was unremarkable. Over the previous six months, K had started to experience numbness in the extremities, uneasiness and general mood changes as he found himself becoming more anxious. The patient stated that the mood changes occurred around the same time as the onset of the headache, and that he was not usually an anxious person. K denied any loss of weight, heat intolerance, change in bowel habit and any history of anxiety disorder or panic attacks. K had no significant family history of hypertension, malignancies, thyroid or heart disorders. K worked as a GP and lived with his wife and two children and reported good family support. He claimed he did not drink alcohol but was a smoker of five pack-years. K denied any illicit drug use. K had no known drug allergies and was not on any regular medication. Review of systems was non-contributory.

On presentation, K was given an urgent appointment for a CT scan which detected a mass in the paraaortic area, caudal to the superior mesenteric artery. He was admitted into the surgical unit for further investigations. At the time of admission, K was apyrexial and had a weight of 71.1kgs, standing blood pressure of 138/82 mmHg and lying blood pressure of 128/82 mmHg. K had a sinus heart rate of 99 beats per minute. He was sweating and looked a little flushed but had a good nutritional state. K did not have any positive findings on clinical examination.

INVESTIGATIONS AND DIAGNOSIS

Although K's history of phaeochromocytoma and his symptoms of headache and palpitations pointed strongly to a recurrence of a phaeochromocytoma, several differential diagnoses were considered, including: (i) anxiety disorder, (ii) carcinoid tumour, (iii) essential hypertension, (iv) hyperthyroidism, (v) migraine, (vi) paroxysmal supraventricular tachycardia, (vii) renovascular hypertension and (viii) insulinoma. Blood was drawn for laboratory investigations which revealed normal full blood counts, renal profile, liver function tests, urea and electrolytes, thyroid function test and blood

sugar. He also had a normal electrocardiogram and urine dipstick showed no abnormalities. The following radiological investigations were carried out, spiral CT of abdomen and chest, I^{131} metaiodobenzylguanidine (MIBG) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) and in order to rule out local adrenal infiltration by the tumour a fine slice helical CT of both adrenals. A 24 hour urine catecholamine collection was also performed.

The results from the spiral CT, MRI, PET and MIBG scan were able to pinpoint the location of a tumour in the area caudal to the superior mesenteric artery called the organ of Zuckerkandl. Fine slice helical CT of both adrenals excluded any involvement of the adrenals. The results also ruled out the existence of metastases. These findings were supported by a positive uptake on the MIBG scan in the paraaortic area and also increased levels of norepinephrine and metanephrines in the urine detected by a 24 hour catecholamine test (see Table 1). The nature of this tumour is to secrete catecholamines periodically, which gives rise

Catecholamine	Conc. in Urine	Normal Range
Norepinephrine	572 nmol	50 – 500 nmol
Epinephrine	2 nmol	5 -120 nmol
Dopamine	12.2 nmol	300–3900 nmol
Metanephrines	1.19 mg	0 – 0.9 mg

Table 1. Results of a 24hr urine catecholamine and metabolite collection for Patient K.

to the biochemical picture depicted in Table 1, in which norepinephrine is raised while epinephrine and dopamine are decreased (probably due to decreased innate production). Metanephrines are always raised in this disease and thus do not depend on periodic secretion.
In some cases 24 hour urine vanillylmandelic acid (VMA) is measured, however it is not measured in this case as urine VMA has been found to be the least specific of the tests available and false positives may arise from coffee, tea, raw fruits and drugs such as (alpha methyldopa). Other tests, such as clonidine and glucagon suppression tests have been used in the past but are no longer common place.

MANAGEMENT

Phaeochromocytomas are amenable to surgical resection and based on the results of our investigations, it was decided that patient K required admission for surgical resection of the phaeochromocytoma. Contraindications to surgery, such as metastatic disease, did not exist.

Pre-operative Management

Before a resection of a phaeochromocytoma, strict surgical criteria must be adhered to ensure the best possible outcome. The main pre-operative preparation before the surgery is adequate adrenergic blockade and adequate hydration of the patient. Patient K was prescribed a non-selective alpha antagonist, oral phenoxybenzamine (which was started at 10mg BD and eventually titrated up to130mg BD) to facilitate complete alpha-blockade in order to prevent a hypertensive crisis during the procedure as manipulation of the tumour may release catecholamines into the blood stream. K was also prescribed a low molecular weight heparin, subcutaneous enoxaparin (40mg OD) for surgical prophylaxis of embolism. The patient was also started on aggressive fluid hydration of normal saline (1L, 4 hourly) to prevent a hypotensive crisis after the removal of the phaeochromocytoma which would cause a sudden drop in the catecholamine levels in the body. K was weighed daily before breakfast and his haematocrit was monitored regularly as a good indicator of sufficient fluid hydration is a 10% increase in body weight and a 10% decrease in haematocrit. K's blood pressure was also taken regularly while lying and standing as a 10% decrease in the blood pressure together with symptoms of postural hypotension was taken as an indication of complete alpha blockage. When the patient was sufficiently hydrated and alpha blocked he was sent for surgery.

Surgical Procedure

Patient K underwent open laparotomy under general anaesthetic. The tumour in the area caudal to the superior mesenteric artery was identified and excised without encountering haemostatic difficulties. The margins were checked and found to be clear and the tumour was sent to the pathology department for further histological staining and microscopy where it was found to be a benign tumour.

Post-operative Management

Post-operatively, K received a detailed management plan. He was admitted into the coronary care unit (CCU) as he required constant 24 hour blood pressure monitoring. This was necessary due the fluctuations in the blood pressure that can occur post resection of a phaeochromocytoma as the body needs to equilibrate to the lesser levels of catecholamine. Urine catecholamines tests were also carried out whilst in CCU to set up a baseline for the catecholamine levels post resection. K also received serial glucose concentration monitoring as there is a risk of rebound hyperinsulinaemia from catecholamine - induced suppression of insulin secretion.

FOLLOW UP AND OUTCOME

Patient K had an normal, uneventful recovery and is doing well. He is seen annually for analysis of 24-hour urinary catecholamines and metanephrines at the outpatient clinic.

DISCUSSION OF PHAEOCHROMOCYTOMA

Introduction

Phaeochromocytomas, first described by Pick in 1912 (1) are rare tumours which secrete catecholamines such as epinephrine and norepinephrine that affect more women than men and have no specific geographical patterns. Phaeochromocytomas are found to be the cause of increased blood pressure in 0.1% of all hypertensive patients (2) and are well known as the "10% tumour". This term was coined due to the nature of the tumour, of which 10% are bilateral, 10% are extra-adrenal, 10% are familial, 10% are in children and 10% are malignant. In this case, patient K is one of the 10% of patients that has the phaeochromocytoma located extra-adrenally. Bilateral

adrenal phaeochromocytomas occur in familial syndromes including multiple endocrine neoplasia (3). Other genetic links with phaeochromocytoma include von Hippel – Lindau gene and the Neurofibromatosis type I gene which is associated with von Recklinghausen's disease. Phaeochromocytomas produce catecholamines and in some cases, adrenocorticotropic hormone, therefore patients may have Cushing's syndrome alongside the clinical symptoms of anxiety attacks, episodic or sustained hypertension (4). Extra adrenal phaeochromocytomas can occur at any site where the chromaffin tissue is located such as the organ of Zuckerkandl as occurs in Patient K's case.

Recurrence

The presented case is an example of a recurrence of a phaeochromocytoma. The incidence of recurrence ranges, from 10% (5) to 60% (6), most of which recur in the five year period following resection. With a vast difference in the recurrence rate, it suggests that malignant tumours might have a higher rate of incidence than previously thought (7). The rate of recurrence depends on several factors: the time of patient follow up and the volume of residual adrenomedullary tissue left post surgery. Therefore, post-operative patients require periodic blood pressure measurements, yearly urinary catecholamine estimations and, where there is a high suspicion of recurrence, an MIBG scan should be carried out.

Complications

The major complications of phaeochromocytomas are associated with hypertension as they cause an increased risk of cerebral haemorrhage, renal dysfunction and myocardial infarction. Other complications include cardiac arrhythmias, hypertensive encephalopathy and heart failure. Interestingly, patients may present with hypotension and shock, which is due to a myriad of reasons such as intravascular volume depletion, abrupt cessation of catecholamine secretion due to tumour necrosis and desensitisation of adrenergic receptors (8).

Prognosis

Prognosis in well prepared patients undergoing resection is good, with low mortality and low morbidity (9). Advances in localisation techniques, medical management and anaesthetic management have resulted in improved surgical outcomes (10). Survival data of patients with malignant phaeochromocytoma is difficult to obtain due to the rarity and indolence of the tumour (11). The Mayo clinic has reported a five year survival rate of 36%, in one study (12) whereas another report showed a five year survival rate of 60% (13). Surgical excision of a benign phaeochromocytoma has a good prognosis as the elective surgery in well prepared patients has low morbidity and mortality rates. Recent papers suggest mortalities between 2 - 4% (14, 15). A review of patients with recurrent phaeochromocytoma showed a five year survival rate of between 32% and 60% (16).

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15-Year-Old Girl with Diarrhoea, Abdominal Pain and Fatigue: A Paediatric Case of Crohn's Disease.

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Clinical Points:

- Crohn's disease (CD) is an immune mediated inflammatory condition.
- Children suffering from CD may present with intestinal or extraintestinal symptoms.
- Useful indicators of CD in children presenting with abdominal pain are: a family history of inflammatory bowel disease, weight loss, growth failure, pallor fatigue, oral ulcers, erythema nodosum, digital clubbing, athralgia, and perianal fistulae or abscesses.
- Growth failure in particular is an important indicator of CD. As many as fifty percent of paediatric patients with CD have a decrease in height velocity before the onset of any other intestinal symptoms.
- Diagnosis of CD involves five steps: clinical suspicion of the illness from history and examination, exclusion of other illnesses that have similar presentation, differentiation between ulcerative colitis and CD, localisation of the diseased region and finally identifying any extraintestinal manifestations of the disease.
- Treatment of the ill patient with active CD typically involves the induction of remission by using potent therapy with a rapid mode of onset. Once remission is induced, the patient can be moved onto a maintenance drug regime.

PRESENTATION OF CASE

A.H., a 15 year old girl presented to casualty with a six week history of worsening diarrhoea, intermittent abdominal pain and fatigue. She described the diarrhoea as loose and mucous-like in consistency without any associated bleeding per rectum, nausea or vomiting. Her abdominal pain had sudden onset and occurred prior to bowel movements. She described it as "crampy" in nature, radiating all over her abdomen and was worst at the upper left quadrant. Pain was rated 8 out of 10 on a scale of 0-10 (with 10 representing the most severe pain) and was relieved by defecation. There were no aggravating or associated features with the pain. She had suffered weight loss of one stone in the six weeks prior to admission with accompanying anorexia. A.H. also had bilateral shoulder and elbow athralgia but did not complain of any rash or episodes of "red eye". She was seen by her general practitioner five weeks prior to presentation to casualty, who suggested that she was suffering from a viral "bug" and that her symptoms would subside. Her weight and height were plotted on a growth chart appropriate for her age and sex. At time of presentation she weighed 39.9 kilograms, which put her below the 3rd centile, and her height was 157cm which is on the 14th centile. There were no previous growth data available. She had pubertal delay and a family history of early menses was noted. A decision was made to admit her.

Upon admission, her vitals were found to be normal. She was apyrexic at 36.6 ^{0}C. Her heart rate was 72 beats per minute and her blood pressure was 115/78 mmHg. Upon inspection, pallor of the palmar creases and aphtous ulcerations in the mouth were noticed. Her abdomen was soft but tender, especially at the left iliac, supra pubic and right iliac area. There were no signs of peritonism or organomegaly and normal bowel sounds were present. Examination of her joints revealed a full range of movement and no tenderness, heat on palpation or signs of inflammation. Assessment of neurological, respiratory and cardiovascular systems were unremarkable. Rectal and peri-anal exams were deferred at this stage.

INVESTIGATIONS AND DIAGNOSIS

The differential diagnoses considered were Crohn's disease (CD), ulcerative colitis, irritable bowel syndrome, coeliac disease, infectious causes (e.g. *Salmonella*, *Campylobacter*, *Clostridium difficile*, *Escherichia coli* 0157:H7 or *Entamoeba histolytica*) and drug-induced colitis (e.g. non steroidal anti inflammatory medications). Rarer diagnoses would include amyloidosis, Whipple's disease and Behçet's disease.

Baseline investigations were performed in casualty and a consultation with the gastroenterology team was requested. Her full blood count was normal with the exception of a reduced haemoglobin level of 10.6 g/dL and an elevated platelet level of 532 X 10^9/L. C-reactive protein was elevated at 110.3 mg/L which was suggestive of active inflammation. Sodium and albumin levels were reduced to 134 mmol/L and 28 mg/L respectively. Infective causes mentioned in the differential diagnosis can mimic symptoms of inflammatory bowel disease and were ruled out by stool culture. A colonoscopy was carried out and biopsies of multiple areas of the colon were taken during the procedure. Abnormalities of the mucosa were noted on the descending and transverse colon and caecum. Aphthous ulcerations, discontinuous colitis with areas of normal mucosa (skip lesions) and a relative reduction of inflammation in the rectum (rectal sparing) were present which, were suggestive of CD. The histological findings were of non-caseating granulomas that were not

adjacent to ruptured crypts. An oesopha-gastro-duodenoscopy with biopsies found that the oesophagus, gastric body, antrum and duodenum had normal mucosa. These findings added weight to the diagnosis of CD. Other investigations that are useful in the diagnosis of CD but were not required in this case, include serological tests (*Saccharomyces cerevise* antibody is usually present in CD while perinuclear antineutrophil cytoplasmic antibodies are negative), barium follow through which can identify areas of narrowing of the intestine, spiral computed tomography scanning which can define the thickness of the bowel wall, mesentery, intra-abdominal and para-intestinal abscesses and pelvic magnetic resonance imaging which is useful if perianal disease is present.

OUTCOME AND FOLLOW UP

A.H. was put on oral prednisolone for three months (1mg/kg/day). After three weeks, the dose was tapered as she was in remission. She was also prescribed a polymeric diet to take once daily. Information regarding long-term complications of CD were discussed with A.H. and her family. Reassurance was given that most complications of the condition can be successfully treated. Four months following admission she was seen as an out-patient and is currently well.

DISCUSSION

Overview of management of CD in a child

The incidence of CD in childhood and adolescence has been estimated to be 3 per 100,000 and has increased during the last decade (1). This has resulted in an increase in the number of clinical trials performed in this area, as current treatment is largely based on data extrapolated from adult trials (2). A multidisciplinary approach is taken in the management of paediatric CD that involves input form paediatricians, gastroentologists, ophthalmologists, general practitioners, nurses, dieticians and psychologists. There are four principle components of a treatment program for a child with CD: i) medical therapy, ii) surgical management, iii) nutritional rehabilitation and iv) psychological support.

Medical therapy administered depends either on the region and severity of the disease or on the type of complication the patient is experiencing (2). Corticosteroids are used to induce remission in moderate to severe CD. Studies have shown that budesonide has a lower toxicity, but lower efficacy compared to prednisolone (2). However long term budesonide use has been associated with growth failure and therefore is only used for short term therapy (not more than four months) (3). Aminosalicylates are indicated for mild mucosal disease in the small bowel and colon. Sulfasalazine is strongly indicated for disease that is limited to the colon whereas mesalamine is best indicated for patients without colonic involvement (2). Azathioprine and 6-Mercaptopurine (6-MP) are thiopurine drugs, and are used for corticosteroid resistant CD. 6-MP is best suited for maintenance of remission and is indicated in refractory CD, fistulating CD or growth failure. Azathioprine is metabolised into 6-MP, therefore these drugs are the same in terms of effectiveness and differ only in their dosing. Side effects include suppression of the immune system which renders patients more prone to infections, pancreatitis, and hepatotoxicity. There is also a very small risk of developing lymphoma (4). Monoclonal antibodies that block tumour necrosis factor α can be used in treatment resistant patients. Infliximab is particularly effective in fistulating CD and its use has been associated with infusion reactions, and infections such as re activation of tuberculosis. A few cases of T-cell lymphoma have been reported (5,6). Methotrexate is indicated, but not often used in refractory CD. Side effects include myelosupression, oral ulcers, infection, hepatitis and pulmonary dysfunction. Antibiotics such as ciprofloxacin and metronidazole are used to treat infectious complications of the disease, such as abdominal or peri-anal abscesses. Intravenous cyclosporin can be used to induce remission in some cases.

Surgical management is reserved for patients that do not respond to medical treatment or develop complications (e.g. fistulas). Surgery is particularly beneficial for patients with limited disease. In severe cases full colonic resection and ileostomy may not be avoidable. Studies have also shown that 6-MP may be the most effective prophylactic agent (7,8).

Nutritional rehabilitation includes primary therapy. This is total enteral nutritional therapy that suppresses inflammation and therefore induces remission of CD (9,10). Partial enteral nutrition is used in patients with growth failure for two reasons; to increase calorie intake and to maintain remission. Supplementation therapy may be given to children with CD who are at risk of micronutrient deficiencies such as vitamins A, D and E, and of zinc, selenium, and folic acid (9,10).

Psychological management may be required in paediatric CD given the chronic and relapsing nature of the disease. It may cause depression (13) or school absenteeism due to increased fatigue or teasing from classmates (14).

Complications

Peri-anal complications such as fissures, ulceration, fistulas, abscesses, and stenosis are often a distressing feature of CD. The majority will heal without treatment, but others may require antibiotics, steroid suppositories, immunomodulators or even surgery. Inflammation of the stomach and duodenum can occur in severe cases of CD which may be treated with oral steroids and immunomodulators (15). Oral lesions such as mucogingivitis, mucosal tags, deep ulceration, cobblestoning and lip swelling occur commonly in children with CD (16,17). A high percentage of patients develop malnutrition, which have undesirable consequences such as delayed growth and puberty in children, decreased ability to tolerate surgery, and psychosocial problems. Osteopenia has been reported (18) and oesteoporosis occurs in up to 30% of children which is due to a combination of factors such as vitamin D deficiency, calcium malabsorption and corticosteroid therapy (19, 20). Other less common complications include uveitis, episcleritis, erythema nodosum and pyoderma gangrenosum.

Prognosis

Unfortunately to date no large-scale multi-centre study has been conducted into the prognosis of children with CD and so we are reliant on data taken from adult trials. CD patients exhibit a widely varying prognosis. Relapsing episodes of varying severity can be a feature. Others may undergo complete remission. Mortality and morbidity is directly related to the complications experienced by the patient. Severe cases may require multiple surgeries that could require lifelong parenteral nutrition dependence.

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A Vision for the Future: Pathology and Emerging Treatments of Age-Related Macular Degeneration

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Clinical Points:

- Two forms of age-related macular degeneration (AMD) exist, a non-exudative form and an exudative form.
- Non-exudative AMD usually presents as slight blurring of central vision and mild metamorphopsia. A central scotoma may develop and progress over years.
- Current management of non-exudative AMD involves little more than advice on risk factor management, however the scene is set for dramatic changes, with Canada pioneering groundbreaking new treatment.
- Exudative AMD typically involves an abrupt onset of blurred central vision, relative or absolute central scotoma, and metamorphosia. Symptoms can deteriorate within days or over months.
- Treatment of exudative AMD has developed rapidly in recent times, and new anti-angiogenic therapies are being increasingly used worldwide.

ABSTRACT
Age-related macular degeneration impacts vastly on elderly populations, particularly in the developed world. The less severe, non-exudative form of the disease is characterised by hypopigmentation of the retina due to atrophic changes in the retinal pigment epithelium. The exudative form is caused by the formation of choroidal neovascular membranes subretinally. Trials of new treatments for the non-exudative form are currently underway and rheopheresis therapy is now available in both Canada and Germany. Treatment of the more severe exudative form has been revolutionised in the past ten years with the advent of transpupillary therapy, intravitreal steroid injections and photodynamic therapy. Most significant is the emergence of anti-angiogenic drugs pegaptanib, ranibizumab and bevacizumab. The future is hopeful, with research ongoing into genetic factors, immunotherapy and new surgical techniques also.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the western world. Of the population over 75 years of age, 3.5% suffer visual impairment due to the disease and this figure is rising (1). In Ireland a 113% increase was seen in the number on the Blind Register due to this condition from 1996 to 2003 (2). While 90% of AMD is classified as non-exudative “dry” AMD, the less common exudative “wet” AMD is more severe. The condition carries with it severe implications for a patient’s quality of life (1). Management of AMD has never achieved much success, and a diagnosis of exudative AMD has virtually been a promise of progression to blindness (3). However, this convention has been obliterated in the past ten years as the world witnessed the birth of a new era for AMD treatment. A myriad of groundbreaking approaches in terms of therapy are being contemplated with an enthusiasm and vigour the condition has never excited before.The purpose of this paper is to broadly explain the pathogenesis of AMD and to provide an understanding of the revolution of its treatment that has occurred in the past decade.

Non-exudative vs Exudative AMD

According to the international classification and grading system for AMD, the condition cannot be diagnosed in individuals younger than fifty years. Non-exudative AMD, also called geographic atrophy, is characterised by the appearance of hypopigmentation of the retina, often juxtafoveally. This form of the disease is relatively slow in its progression, with the development of blindness taking several years after the disease has been identified in both eyes. In contrast, exudative AMD, also known as neovascular AMD, follows a much more rapid course and is therefore acknowledged as being the more severe of the two. It is recognised by the appearance of choroidal neovascular (CNV) membranes and the accumulation of subretinal haemorrhages and scarring which can progress within days or months. Blindness usually occurs in a matter of months if both eyes are affected by exudative AMD.

PATHOLOGY

The pathology of AMD centres on age-related changes in Ruysch’s complex located at the outer retina (the retinal layer adjacent to the choroid layer) (4). Ruysch’s complex comprises the retinal pigment epithelium (RPE), Bruch’s membrane and the choriocapillaries (see Fig.1.).

RPE and Dry AMD

The RPE carries out several important functions, most notably regeneration of rhodopsin (the photoreceptor pigment) and phagocytosis of old photoreceptor components. The accumulation of lipofuscin (a “wear and tear”/ “aging” pigment) in the RPE cells compromise this phagocytic function (5). In addition, lipofuscin contains the compound A2E (a by-product of rhodopsin recycling). A2E inhibits the lysosomal proton pump resulting in leakage of lysosomal contents which ultimately leads to cell death. The resulting decrease in the RPE cell population increases the workload of the remaining RPE cells, further

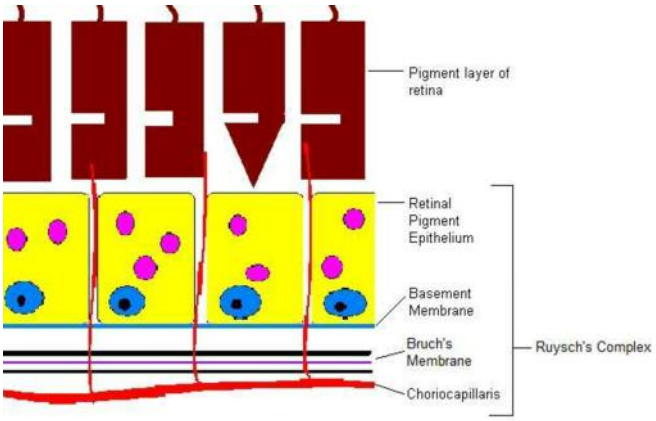

Fig. 1. Illustration of the outer layer of the retina and Ruysch's complex. Lipofuscin accumulates in the lysosomes of the RPE cells with increasing age. The potential space between the RPE Basement Membrane and Bruch's Membrane is the site of drusen accumulation in dry AMD and the site of CNV formation in wet AMD.

compromising their function. This is particularly prominent in the para-foveal regions involved in dry AMD (6). The death of RPE cells results in loss of lipofuscin, giving rise to the areas of hypopigmentation characteristic of dry AMD.

Bruch's Membrane and Dry AMD

Bruch's membrane, secreted by and lying external to the RPE, is made up of two collagenous layers enclosing a central elastic layer. The potential space between the basement membrane of the RPE and Bruch's membrane is the site of accumulation of drusen (7). The pathogenesis of this accumulation is not understood but it is noted that the substance, made up of a glycoprotein core, RPE debris, and other proteins, including inflammatory proteins (8), induces a chronic inflammation in the area causing further damage to tissue.

Hypoxic Changes and Wet AMD

Exudative or neovascular AMD is thought to result from hypoxic changes in the retina (4). Hypoxia ensues when the blood supply of the retina, coming entirely from the choriocapillaris, is compromised due to a combination of decreasing lumen diameter of the vessels and decreasing permeability of Bruch's membrane (due to rising lipid content and membrane thickening) as happens with advancing age (9). Hypoxia induces production of various growth factors in the retina. Of note is the production of Vascular Endothelial Growth Factor (VEGF) on the external side of the RPE, adjacent to Bruch's membrane (10). VEGF, which promotes angiogenesis, is thought to be responsible for the invasion of this plane by new vessels branching from the choriocapillaris, forming the choroidal neovascular (CNV) membrane (11). The new subretinal vessels tend to grow in centripetal fashion toward the fovea. As the thickness of the elastic layer of Bruch's membrane in the fovea is approximately one third that in the peripheral retina, it is hypothesised that this growth pattern may simply be following the path of least tissue resistance (4). CNV membrane development leads to exudation, bleeding and scarring (12). The accumulation of serous or haemorrhagic fluid can then cause the RPE to detach from Bruch's membrane, accounting for the rapid deterioration in visual acuity seen with the exudative form of the disease (4).

TREATMENT

Ten years has seen major advances in the treatment of AMD. Exudative AMD, as the more severe form of the disease, has received the most attention, with exciting new therapies showing great promise for the future. Since 2003, however, dry AMD has become the focus of some interesting trials using novel approaches.

Treatment of Non-Exudative AMD

Current treatments for non-exudative or dry AMD are scarce. Essentially, little can be done beyond risk factor control (1). Patients are advised to stop smoking, to keep blood pressure under control and to eat a diet high in carotenoids (a retinal pigment component), high in antioxidants and low in fat. A randomised controlled trial currently underway is suggesting that substantial benefits can be derived from dietary supplementation with the antioxidant lutein also (13,14). Other trials are investigating a number of novel treatments for dry AMD (15). Rheopheresis, a technique used to filter larger proteins from the circulating blood, is proposed to reduce progression of dry AMD by enhancing the microcirculation of the choriocapillaries (16). This treatment option for dry AMD is currently approved in Canada, a decision justified by interim reports from a double-blind, randomised, multi-centre clinical trial (The Multicenter Investigation of Rheopheresis for AMD) (17). The success of a number of trials currently underway is likely to determine whether rheopheresis will be approved by both the FDA and the European Commission (15). Oral fenretinide decreases serum retinol (a compound present in rhodopsin). This decreases the production of A2E (the toxic lipofuscin component that is a by-product of rhodopsin recycling) and slows the process of geographical atrophy. Results of a Phase II trial investigating this novel approach to treatment are expected in 2009 (18).

Treatment of Exudative AMD

Conventional treatments for the more severe exudative form or wet AMD are limited at best (19). Irradiation of the CNV membrane with argon laser, for example, first reported in the 1980s, leaves the patient with significant damage to the overlying retina (20). Removal of CNV membranes using subretinal surgery did not benefit the vast majority of patients, despite some success stories (21). Over the past ten years, however, sophisticated treatments have been developed to treat this disease (4).

Transpupillary thermotherapy (TTT), a process which targets the CNV membrane vessels with infrared diode laser energy to occlude the vessels (with the infrared wavelength used minimising thermal injury to the overlying retina), was found to decrease exudation in several uncontrolled trials and analyses (22,23). However, benefits of TTT were called into question when a randomised, double-blind, placebo-controlled trial involving 303 patients published in 2002 failed to show a statistical difference between it and sham treatment (24). Intravitreal injection of steroids such as triamcinolone acetonide is also used to

slow progression of wet AMD (25). In addition to having angiostatic properties that cause recession of the CNV membrane, triamcinolone suppresses the chronic inflammation present in Ruysch's complex. Preclinical studies demonstrated inhibition of laser-induced neovascularisation (26,27). A non-randomised controlled clinical intervention study following patients receiving both the intravitreal injection and placebo for several months saw significant improvements in visual acuity at one and three months (28). However, long term follow-up failed to confirm the benefits of this treatment over placebo. These findings echoed those of a randomised, placebo-controlled clinical trial previously completed (29). In addition to the questionable benefit of these injections, there is also a significant risk of eye-related side effects including endophthalmitis, cataract formation and increases in intraocular pressure (30). Despite this, intravitreal corticosteroids are commonly used in wet AMD (3).

The benefit of photodynamic therapy (PDT) in the treatment of exudative AMD, in contrast, has been demonstrated in numerous randomised, placebo-controlled trials (31,32). This treatment consists of the intravenous administration of verteporfin (trade name Visudyne), a light-sensitising dye which becomes concentrated in the rapidly dividing cells of the CNV membrane, followed by irradiation of the area with a diode laser, using fluorescein angiography to visualise the CNV membrane. The laser activates the verteporfin dye causing the release of free radicals that damage the endothelium of the CNV membrane and cause thrombosis of its vessels, thus selectively destroying the membrane while leaving the surrounding normal retina unharmed (1). While the procedure does create a small scotoma, it is far less than would result from the disease being left untreated. However, as with the treatments described above, the benefit of PDT lies only in its ability to slow down the rapidly progressive course of exudative AMD (3), and CNV membrane recurrence is common (1).

Anti-Angiogenic Treatments

Unquestionably, anti-angiogenic therapy is the most revolutionary treatment for exudative AMD that has emerged to date .

Pegaptanib

Pegaptanib sodium was the first of the anti-VEGF drugs to win the approval of the United States Food and Drug Administration (FDA) for the treatment of wet AMD (33). An inhibitor of VEGF-165 (the most important of the five VEGF isotypes present in the human eye), it is injected into the vitreous humor of the eye. Approval from the European Medicines Agency (EMEA) came in 2006 (33) following the VISION Study Group's two randomised, multi-centre, double-blind trials that demonstrated a 27% treatment benefit of pegaptanib therapy over PDT (2,34). The groundbreaking nature of this approach to AMD treatment, however, lay in the finding that it gave rise to an increase in visual acuity from baseline in more than 20% of those treated (1,34). As all other treatments options serve only to slow progression of the disease, the advent of a therapy that can potentially cause regression of neovascularisation is inspiring, and the area of anti-angiogenesis is being investigated with vigour. In spite of this statistical success, however, pegaptanib does not arrest vision loss in many patients, raising doubts in some regarding its clinical benefits (3,35). An answer to this problem lay in the development of ranibizumab, a mouse/human monoclonal antibody fragment, demonstrating pan-blockade of all forms of VEGF (1,19).

Ranibizumab

The ANCHOR Study Group (ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD) demonstrated the significant efficacy of ranibizumab with a randomised, double-blind, multi-centre study (36). Ninety-five percent of treated eyes did not experience significant progression of disease (defined as the loss of more than three lines on the standard visual acuity chart) at one year compared to 62% of controls (who were undergoing PDT). In contrast, the VISION Study Group (The VEGF Inhibition Study in Ocular Neovascularisation) had found that disease progression was prevented in only 70% of eyes treated with pegaptanib compared to 55% of controls (also undergoing PDT) (34). In addition to this triumph, an improvement in visual acuity from baseline was seen in 34% of eyes treated with ranibizumab compared 5% of controls (36). The drug, administered as monthly intravitreal injections, was approved for the treatment of wet AMD by the FDA in June 2006 and by the EMEA in January 2007 (33).

Bevacizumab

Currently, interest in the use of the full-length anti-VEGF mouse/human antibody bevacizumab is growing. This is fuelled in no small part by the significantly lower cost of the whole antibody (37,38), particularly following controversy that erupted in 2007 and forced the National Institute for Health and Clinical Excellence in the UK to review its final decision regarding the eligibility of ranibizumab for National Health Service funding (39).Bevacizumab, which has been licensed for the treatment of various cancers since 2004 (40), was first evaluated as a possible treatment for AMD in an open-label, single-centre, uncontrolled trial which found significant increases in visual acuity after twelve weeks of intravenous administration of the drug (41). In subsequent studies, intravitreal administration has been used, resulting in a lower incidence of systemic side effects (42). Some concerns, such as the likelihood of increased antigenicity, have been raised regarding possible side effects of the whole antibody in comparison to the partial antibody ranibizumab. Several small studies, including a retrospective case series undertaken by an Irish group, have demonstrated significant benefit associated with bevacizumab (43,44). However, at present, no large-scale, randomised trials have been carried out on the efficacy of the treatment. Despite this, and despite the fact that bevacizumab has yet to be granted either EMEA or FDA approval (1,45), its low cost price has led to it being commonly used in the treatment of exudative AMD worldwide.

CONCLUSION

The face of age-related macular degeneration is changing rapidly with the recent advent of exciting new treatments for the severe exudative form and with novel treatments being investigated for the more common non-exudative form. Certainly, further research is warranted with randomised clinical trials of bevacizumab being very much called for as it is potentially the most cost-effective treatment available for neovascular AMD. Recently, research has been directed toward the genetics of the disease which may provide clues to other possible lines of treatment. Current trials are investigating the possibilities of immunotherapy, anti-pigment epithelium derived growth factor therapy and macular translocation surgery amongst others. We are entering into a new era of interest and enthusiasm for research into this disease. We can assure ourselves that the situation is growing brighter for those who, a mere ten years ago, would have been facing no vision for the future.

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Vitamin B12 Deficiency: Causes, Evaluation and Treatment.

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Clinical Points:

- Deficiency of serum vitamin B12 levels can cause a variety of neurological and psychiatric disorders.
- Vitamin B12 deficiency has been reported in approximately 15% of adults older than 65 years of age. This is believed to be mainly caused by an age-related decline in intestinal absorption.
- Approximately 98% of B12 absorption is facilitated by intrinsic factor. The remaining 2% is absorbed passively.
- Oral B12 supplementation in high doses has been found to be as effective as intra-muscular vitamin B12 administration in pernicious anaemia.
- Intra-muscular B12 remains the treatment of choice in most Western countries, contrary to the prevailing evidence.

ABSTRACT

Vitamin B12 (cobalamin) deficiency is a major public health problem, particularly among the elderly population. It is known that a deficiency in serum B12 levels can cause a combination of neurological and psychiatric disorders. Therefore, in these cases successful replacement of depleted B12 levels is a necessity. Identification of B12 deficiency in elderly patients can be rather difficult as they often tend to present with neurological and neuropsychiatric symptoms despite a lack of haematological evidence showing depleted serum B12 levels. More recently, other parameters such as methylmalonyl-CoA or homocysteine (components of the cobalamin-dependent pathways) have been used as markers of B12 deficiency. Both parameters become elevated upon the onset of B12 deficiency. Several studies have shown that oral B12 replacement therapy can be equally as effective as parenteral (intra-muscular) B12 replacement. Yet, despite these publications, B12 is primarily administered to deficient patients intramuscularly. This inconvenient method of B12 replacement places a rather unnecessary demand on healthcare resources.

INTRODUCTION

The neurological disorders associated with vitamin B12 deficiency have previously been well described (1). It is known that patients with low serum B12 may have neurological complications as a result (2), in which both the central nervous system and peripheral nervous system are affected. A deficiency in vitamin B12 may cause autonomic failure (1). This review aims to discuss the causes, evaluation and treatment of a deficiency in serum B12 levels. A remarkable therapeutic trial that was previously carried out, in an effort to treat the once-fatal condition known as pernicious anaemia (common in patients with B12 deficiency), will also be discussed.

NORMAL B12 ABSORPTION

Vitamin B12 (cobalamin) plays an important role in DNA synthesis and neurological function (3). Adequate serum levels are necessary for nervous system maintenance and the development of normal red blood cells (4). Vitamin B12 cannot be synthesised in the body and must therefore be obtained from the diet. The main dietary sources of B12 are dairy products, meat (especially liver) and eggs. The acidic environment of the stomach enables the release of B12 that is bound to food (3). The free B12 is then rapidly bound by intrinsic factor (IF), a muco-polysaccharide secreted by the gastric parietal cells that line the stomach. The binding of B12 to IF occurs in the duodenum causing the formation of the IF-B12 complex (4). This complex is resistant to digestion by gastric juices. Upon reaching the terminal ileum, it binds to and is absorbed by the intestinal microvilli. In the plasma, about 20% of the absorbed B12 binds to the serum protein holotranscobalamin (Holo-TC) for transport (5). Holo-TC is the protein that delivers bound B12 to all cells in the body. The majority of B12 (80%) circulating in the blood binds to the serum protein haptocorrin and is biologically unavailable for most cells (6). The function of haptocorrin remains unknown.

Only two enzymatic reactions are known to be dependant on B12 in humans, which are the conversion of methylmalonyl-CoA to succinyl-CoA (a necessary component of the citric acid cycle) and the conversion of homocysteine to methionine (3). The latter reaction is accompanied by the conversion of methyltetrahydrofolate to tetrahydrofolate, which is necessary for efficient DNA synthesis (6). Therefore, a deficiency in B12 can impair DNA synthesis.

CAUSES OF VITAMIN B12 DEFICIENCY

The causes of vitamin B12 deficiency can be divided into three classes: i) nutritional deficiency, ii) malabsorption syndromes and iii) other gastrointestinal (GI) causes. (7)

Nutritional Deficiency

Nutritional deficiency of B12 can occur in specific populations. The elderly, chronic alcoholics and vegans are most at risk due to the dietary deficits of B12 frequently found within these groups.

Malabsorption Syndromes

The primary example of a malabsorption syndrome is pernicious anaemia. This condition is the result of an autoimmune disease in which antibodies attack the parietal cells of the stomach, almost completely blocking the

release of IF as a result. This hindered IF release prevents the formation of the IF-B12 complex, subsequently impairing B12 absorption. Researchers now believe there is an age-associated decline in the intestinal absorption of B12 (5). Therefore, it comes as no surprise that B12 deficiency has been reported in about 15% of adults older than 65 years (3).

Other GI Causes

Although quite rare, certain GI conditions can also cause B12 deficiency. If a patient has an intestinal parasite infestation such as *Diphyllobothrium latum* (fish tapeworm) this may compete with the intestinal microvilli for the absorption of B12 (7). Similarly, if a patient has a bacterial overgrowth in the small bowel (commonly seen in those with a history of intestinal surgery), it would also compete with the ileum for the absorption of B12 (3).

EVALUATION OF VITAMIN B12 DEFICIENCY

Problems arise immediately when trying to define vitamin B12 deficiency. The scientific literature uses pmol L^{-1} while clinical laboratories use ng L^{-1} (8). It has been argued, that while serum holotranscobalamin levels may give an indication of the absorption of B12, malabsorption and deficiency are separate entities (9). Therefore, numerous attempts have been made to qualify B12 deficiency as either clinically or metabolically significant by including other parameters such as methylmalonyl-CoA or homocysteine (components of the cobalamin-dependent pathways). If these components are found to be elevated above normal it would indicate a "tissue deficiency" even if serum B12 is found to be normal (10).

In 2006, Dr. Harold Hin and his colleagues carried out the "Banbury B12 study". This cross-sectional study examined associations of cognitive impairment, depression and neuropathy with blood measurements of B12 in elderly people. A total of 1,000 community-dwelling individuals over the age of seventy five years were examined. In this study, participants with a serum B12 concentration of less that 133 pmol L^{-1} were deemed to be B12 deficient. Low B12 concentrations were identified in 13% (125 participants) of this free-living population. Cognitive function was assessed using the Mini-Mental State Examination and a Hospital Anxiety and Depression test was used to assess depression. The results from these standard tests indicated that low B12 concentrations correlated with cognitive impairment and depression. A further finding was that participants with B12 levels in the bottom quartile had a two-fold risk of cognitive impairment, when compared to those in the top quartile. Low B12 levels were also associated with peripheral neuropathy, based on the findings that the B12 deficient participants were observed to have missing knee and ankle jerk reflexes (11).

HISTORY OF PERNICIOUS ANAEMIA TREATMENTS

B12 deficiency can cause several forms of anaemia, most notably pernicious anaemia. The story behind the earlier treatments of pernicious anaemia is a rather fascinating one. Up until the late 1920's pernicious anaemia was untreatable and fatal. Three American physiologists (William Murphy, George Minot and George Whipple) devised the concept that food could be used to treat pernicious anaemia. The diet they constructed containing liver "in such quantities [that] seemed very outrageous" had dramatic beneficial effects on the once untreatable pernicious anaemia (12). In 1934, the three colleagues were awarded the Nobel Prize in physiology and medicine.

Despite the proven efficacy of the liver therapy, a more satisfactory method of treatment than the daily consumption of a half pound of liver was needed. An American doctor named William Bosworth Castle devised an idea that enabled him to investigate the pathophysiology of this disease. Liver seemed to be necessary for the patients' bone marrow to function properly and Castle questioned why normal people did not have to eat such large amounts of liver to stave off pernicious anaemia. He attained permission from his supervisor (the aforementioned Dr. Minot) to carry out a rather unusual therapeutic trial. This investigation required Castle to consume 300g of rare hamburg steak daily for ten days. An hour after eating (thereby ensuring the gastric juices were adequately mixed with the ingested food), he would then regurgitate his stomach contents and incubate them until they had liquefied. Castle then directly administered the mixture to the stomach of patients suffering from pernicious anaemia via a flexible tube. Amazingly a clinical improvement and a reticulocyte increase were observed in all of the patients tested. Castle proposed a theory that an "intrinsic factor" is secreted by the stomach of normal healthy individuals which is required for the formation of an "anti-pernicious anaemia complex [from an] extrinsic factor", present in beef and liver (13).

The B12 molecule was first isolated in its cyano-form in 1948 (14) and was then identified as the active component of the "extrinsic factor" proposed by Castle. The chemical structure of the B12 molecule was later confirmed, using x-ray crystallography by Dorothy Hodgkin in 1956. She was subsequantly awarded the Nobel Prize in chemistry for her significant findings.

CURRENT TREATMENTS OF B12 DEFICIENCY

B12 supplementation is now widely used for the treatment of B12 deficiency (4). Currently, most B12 deficient individuals are treated with an intramuscular B12 injection. (4) This is highly surprising, considering case-series and case-control studies, dating as far back as the early fifties, have shown oral B12 supplementation to be equally as effective as intra-muscular B12 administration (15). Recent studies have also reached similar conclusions. For example, in 1998, Kuzminski et al. performed a randomised trial on 38 vitamin B12 deficient patients. Participants received either oral or intra-muscular B12 supplementation for 120 days. Differences dosages were administered to each group. Patients in the oral supplementation group received daily dosages of 2,000 mcg of B12 for 120 days, whereas patients in the parenteral group were intra-muscularly injected with 1,000 mcg on days 1, 3, 7, 10, 14, 21, 30, 60 and 90. Once the 120 days had elapsed, haematological testing revealed that patients in the orally supplemented group had considerably higher serum B12 levels than those the intra-muscularly injected group (16).

The transport mechanism for absorbtion of oral B12 that has been proposed by researchers is that B12 can actually be absorbed both actively (upon binding to IF) and passively (without binding to IF) (17). It is now known that B12 is primarily absorbed actively but the passive mechanism accounts for 1-2% of absorption (17). Therefore, it is believed that oral replacement therapy can be as effective as parenteral supplementation, provided that B12 is administered at a sufficient dose (3).

There are disadvantages associated with intra-muscular B12 supplementation when compared with oral B12 supplementation. Firstly, injections can be quite painful and distressful for patients and can therefore become a considerable source of work for healthcare professionals (18). Secondly, injections must be administered in either a healthcare facility or in the home of the patient, by a visiting healthcare professional (19) which can place a demand on healthcare resources that may be avoided with oral supplementation.

It remains highly surprising that oral B12 supplements are rarely prescribed to B12 deficient patients, despite the evidence. This is most likely because many clinicians are unaware that oral B12 supplementation can be as effective as intramuscular injections, provided they are taken in sufficiently high dosages (3). Only Canada and Sweden have successfully reversed their method of treatment from parenteral to oral supplementation, which now accounts for 73% of B12 replacement in these countries (20).

SUMMARY

Healthcare professionals should be made aware that high-dose oral supplementation can be equally as effective as intramuscular injection, when used to treat patients with a B12 deficiency. The oral method of supplementation has been shown to be safe, cost effective and well-tolerated by patients (21). This form of treatment would be less distressful for patients and far less resource-consuming on the healthcare system.

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Treatment of Basal Cell Carcinoma: A Focus on the Role of Mohs Micrographic Surgery

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Clinical Points:

- Basal Cell Carcinoma (BCC) is the most common cancer worldwide and is most likely to occur on the sun-exposed areas of the head and neck in fair-skinned patients over the age of forty.
- While almost never metastasising, it can be extremely locally invasive and cause functional and cosmetic compromise.
- Mohs Micrographic Surgery is a specialised technique used to treat BCCs in which horizontal slices of the excised tissue are examined microscopically as opposed to the typical vertical slices of standard surgery.
- This allows for examination of 100% of the margins to look for residual tumours and therefore decreases the likelihood of recurrence and increases tissue sparing which is essential for a good cosmetic result.

ABSTRACT
Basal Cell Carcinoma (BCC) is the most common cancer in human and the leading cutaneous malignancy of the fair skinned Irish population. Mohs Micrographic Surgery is a specialised operational technique used in the treatment of BCC. It involves excision of the cancer and microscopic examination of 100% of the surgical margins. It has the highest cure rate of any treatment for BCC and the best cosmetic outcome as it does not sacrifice unnecessary surrounding tissue.

INTRODUCTION
Basal Cell Carcinoma (BCC) is a malignant neoplasm of epithelial cells, making up about 75% of all nonmelanoma skin cancers. It is the most common human malignancy (1). There are three main histological types: 1) nodular BCC, also known as “rodent ulcer”, accounting for 60% of all BCCs, 2) superficial BCC, which is the next most common, comprising up to 15% of all BCCs (2) and 3) sclerosing/ morpheaform BCC. In general, BCC is not an aggressive form of cancer, remaining localised with a very low rate of metastases (0.0028% to 0.55%) (3). However, if neglected, BCCs persist, enlarge, ulcerate and subsequently invade and destroy surrounding structures which may result in significant functional and cosmetic morbidity. The clinical course is generally unpredictable with aggressive, rapid extension from the outset, with the tumour growing only gradually or in spurts punctuated by partial regression (4).

Although BCCs can occur anywhere on the body, up to 85% are encountered on sun-exposed areas such as the face, scalp, ears and neck. Of these, the nose is the most commonly affected site, accounting for 25-30% of all BCCs. BCCs may occasionally complicate venous stasis ulcers, arteriovenous (AV) malformations, port wine stains or skin/hair graft transplantations or arise from scars of variable aetiology e.g. surgical, burn, post vaccination or post infection by *Leishmania* or *Varicella* (5).

The relationship of exposure to ultraviolet (UV) light, which is the most important risk factor, and development of BCCs is complex; showing strong associations to intermittent (recreational) sun exposure, especially exposure in early life (6). Those with fair skin (skin types 1 and 2) are at highest risk; particularly those of Scottish, Celtic or Scandinavian descent (7). BCCs can occur at any age but incidence increases after forty years of age (8) and men are slightly more commonly affected than women (1.2:1) (9). A UK study also indicates that higher social classes are also at increased risk (10). In this review, the treatment of BCC with a specific look at Mohs Micrographic Surgery (MMS) is discussed.

WHAT ARE THE TREATMENTS FOR BCC?
Both medical and surgical treatment options for BCC are available (2). Medical treatments include radiation therapy, CO2 laser treatment, photodynamic therapy, topical and intralesional chemotherapy with 5-fluorouracil and intralesional chemotherapy with interferon alpha or imiquimod. Surgical options include standard surgical excision, which is the most commonly used method (11), cryosurgery, curettage and electrodessication (C & E) and MMS.

According to a recent review (12) which compared these treatment modalities *radiation therapy* demonstrates five year cure rates (FYCR) of 90-93% in small, localised tumours, however it is less successful in the treatment of larger or invasive BCC. It also has a less favourable cosmetic outcome compared to C & E and surgical excision. *Photodynamic therapy* and topical intralesional chemotherapy with 5-fluorouracil are both only suitable for use in superficial tumours, as success is limited by their depth of penetration. *Imiquimod*, as monotherapy, has lower success rates in eradicating BCC compared to surgical excision, C & E and MMS, however it can improve the cure rates of other treatment modalities if used as an adjuvant. *Cryosurgery* has a FYCR of 93% for BCC. *C & E* has an FYCR of 92% in primary BCC, which varies depending on tumour size and is more successful in the treatment of small, localised tumours. *Standard surgical excision* has FYCR of 95% for primary BCC and 83% if recurrent BCC. The technique, although a cost-effective and usually successful method for treatment of low-risk tumours, does not involve histological examination of 100%

of the surgical margin and there is increased risk of recurrence in high risk BCC. *MMS* is the gold standard treatment for BCC (12), with a recurrence rate of only 1% in primary BCC. Although it may cost more than other methods, this may be mitigated by a reduction in tumour recurrence and the costs of re-treatment. Other studies have found that MMS has the lowest recurrence rates when compared to all other treatment modalities, especially in the case of recurrent BCC (13), where rates are only 6-10% (14).

WHAT IS MMS AND WHY IS IT SUITABLE FOR TREATMENT OF BCC?

Classical chemosurgery, the technique which later evolved into MMS, was first described in 1941 by Dr Frederick E Mohs. MMS is a highly specialised operative technique used in the removal of high risk BCC and many other cutaneous lesions e.g. squamous cell carcinoma (depending on type and location), keratoacanthoma, dermatofibrosarcoma protuberans and verrucous carcinoma (see Table 1) (15). It is performed as a day case under local anaesthetic by a dermatologist who has undergone additional training in a one to two year fellowship, rather than by a surgeon because of the necessary understanding of pathology and cutaneous oncology.

Two major innovations were characteristic of Mohs original technique:

i)Examination of 100% of the excised tissue margin, as opposed to the standard vertical “breadloaf” technique which may only allow 0.1% of the surgical margin to be examined (16).

ii)Preference for healing by second intention, that is, without wound closure, which results in a more acceptable cosmetic result, particularly on concave areas (2). This is still a simple, cost-effective choice today (preferred method of wound repair in 23-33% of cases) despite the predominance of more complex methods of wound repair (17).

MMS is a very suitable a treatment for BCC due to the careful mapping technique and horizontal sectioning. Minimal sacrifice of normal tissue allows retention of function and optimal cosmetic results on the areas affected, which with BCCs are most likely the head and neck, regions of great aesthetic importance to the patient. The procedure is carried out in stages, or Mohs layers, in which successive layers of tissue are excised and examined microscopically for residual tumour. The number of layers required to remove the tumour depends on its subclinical extension (18). MMS is constantly evolving and there have been a number of recent exciting developments regarding the standard technique, including employment of immunohistochemical stains to improve visualisation of tumour extension (19), the intra-operative delineation of tumour margins using multispectral dye enhanced polarized light imaging (20) and the use of real-time confocal reflectance microscopy to obviate the need for creation of frozen sections (21).

- •Recurrent non-melanoma tumour (especially common in the “H” zone of the face where embryonic fusion planes meet and where sacrifice of the least amount of uninvolved tissue is paramount)
- •Large tumours (>2cm)
- •In high risk anatomic locations (periorbital, perinasal, preauricular, perioral)
- •In aggressive histological subtypes (morpheaform/ sclerosing,metatypical, micronodular, or fibrosing BCC)
- •In anatomic sites where tissue preservation is imperative (fingers, genitals)
- •Tumours with poorly defined clinical borders
- •Tumours arising in irradiated skin
- •In immunosuppressed patients
- •Tumours with positive margins on prior excision (incompletely excised lesion)
- •Tumours in chronic scar (Marjolin’s ulcer)
- •Naevoid BCC syndrome
- •Tumours in Xeroderma pigmentosum
- •In perineural invasion
- •Tumours in Bazex syndrome

Table 1: **Indications for MMS in the treatment of BCC.**
Adapted from Dermatology, Bolognia et al, 2003 (2)

MMS METHOD (22, 23)

MMS begins with excision of a previously debulked (by curettage) tumour and a variable margin of normal appearing surrounding skin using a scalpel angled at 45 degrees away from the tumour. This allows a progressively more bevelled incision with eventual undercutting of the tumour so that the excised tissue is saucer shaped (see Fig.1A.). The specimen and surrounding skin are marked with scalpel cuts (hash marks) for orientation prior to removal (see Fig.1B.) and are carefully plotted on a micrographic map. The wound is dressed and the patient returns to the waiting room while the specimen is processed by the histotechnician. This involves dividing it along the hash marks, usually into 2-4 pieces of 0.5-1.5 cm each (see Fig.1C.), using coloured dyes e.g. merbromin

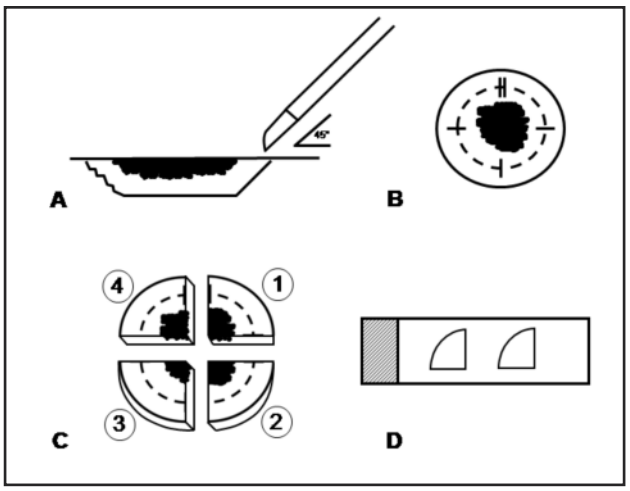

Fig. 1. **Overview of steps in Mohs Micrographic Surgery.**

(Mercurochrome) to mark the non-epidermal edges to preserve proper orientation (noting this on the map also), and subsequently inverting it and using a heat extractor to embed it deep side up in an optimum cutting temperature compound. This flattens it such that the epidermal margin and the deep tissue plane are on the same level. A cryostat is then used to cut 4-7 micrometre frozen sections, which are assembled on slides from deep to superficial and examined under the microscope (see Fig.1D.).

If residual tumour is found, it is noted on the map and a subsequent Mohs layer is done, re-anaesthetising the patient and removing additional tissue only from the area indicated on the map to contain residual tumour. This process is repeated until all margins are free of tumour. The wound is then either dressed and allowed to heal by second intention or closed immediately, using primary layered closure or local skin flaps and grafts, followed later by further reconstruction if necessary. Post-operative radiation therapy may be indicated in cases where complete tumour clearance is unachievable.

Post operative reviews are carried out at six weeks to ensure proper wound healing and contraction and at three months to monitor recurrence. During this time, patient education regarding limiting UV exposure is important. Annual surveillance for new primary and recurrent cancer is recommended for all patients, given that 30-50% of those with non-melanoma skin cancer will experience another skin cancer within five years (24).

COMPLICATIONS OF MMS

Complications with MMS are rare; evaluation of 1358 consecutive cases in the Duke University MMS unit revealed a low incidence of surgical complications (1.64%), mainly involving haemostasis (25). Intraoperative complications include anxiety, pain due to local anaesthetic injection, bleeding, nerve damage (sensory/ motor), particularly with BCCs located in the vicinity of the temporal branch of the facial nerve and allergic reactions. Careful preoperative assessment of the patient and planning of the procedure can do much to avoid these complications.

Post operative complications include post operative bleeding, haematoma/seroma formation, infection, necrosis, wound dehiscence and scarring. The incidence of these complications may be reduced by meticulous haemostasis during surgery, pressure bandages and post operative wound care by the patient. The rate of clinically significant infection after MMS is very low (only one patient in the Duke University MMS study) but prophylactic antibiotics may be prescribed if deemed necessary due to tumour site.

COST-EFFECTIVENESS OF MMS

Due to the fact that increased resources are required in order to perform MMS, it is argued that the expense in terms of both the time and money involved precludes its widespread introduction as first line treatment for BCCs over SSE. A recent Dutch study concluded that MMS was not a cost-effective treatment of either primary or recurrent BCCs, with a mean difference in total costs of €254 for primary BCCs and €249 for secondary BCCs for MMS versus standard surgical excision (26). The mean total cost of BCC removal using MMS was €1137 for primary BCCs and €1146 for recurrent BCCs. Total costs included pre-operative, theatre-related and post-operative costs. However several limitations of this study have been pointed out (27, 28) and further studies are required.

CONCLUSION

MMS is evolving as a surgical technique that will be increasingly in demand with the epidemic rise in cutaneous cancers in Ireland. Despite this evolution, the two basic principles guiding MMS since its inception are maintained – precise margin control and tissue conservation. MMS is predicted to remain the gold standard for removal of non-melanoma skin cancers such as BCC.

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The Modern Methods in the Surgical Reconstruction and Rehabilitation of the Orofacial Region: A Review of the Literature

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Clinical Points:

- Advances in the reconstruction of defects in the orofacial are now carried out by use of microvascular free tissue transfer, osseointegration of dental implants and the use of new bone growth promoting substances.
- Microvascular free tissue transfer is a highly successful technique that involves harvesting of tissue from distant sites for reconstruction via re-anastomosis of tissue blood vessels to vessels in the recipient area.
- Prosthetic rehabilitation is carried out via dental implants, which can integrate with bone (osseointegration), and is followed by construction of dental prostheses.
- The use of scaffold materials, growth factors, distraction osteogenesis and alloplastic materials are advances that may prove beneficial with further research and development.

ABSTRACT
Maxillofacial and dental defects often cause detrimental effects to patient health and appearance. A holistic approach of restoring lost dentition along with bone and soft tissue is now the standard treatment of these defects. Recent improvements in reconstructive techniques over the past number of decades especially osseointegration, microvascular free tissue transfer and improvements in bone engineering have yielded excellent functional and aesthetic outcomes. This article reviews the literature on these modern reconstructive and rehabilitation techniques.

INTRODUCTION
Reconstructive maxillofacial surgery refers to the wide range of procedures designed to rebuild or enhance soft or hard tissue structures of the maxillofacial region. Reconstructions of jaw and mouth defects represent a challenge to the surgeon (1,2,3,4,5) and are most commonly indicated in patients with oral squamous cell carcinoma (SCC). They are also used in cases of benign tumours, trauma, osteoradionecrosis, infection, chronic non-union of bone, clefts, congenital deformities and old age (5,6,7). The development of antibiotics, improved diagnostic imaging and anaesthesia have heralded a new era of success in maxillofacial reconstruction (1,2,4,6). In the past twenty years, the development of bone technology (8,9,10,11,12), osseointegration (13,14,15,16,17) and microsurgery (7,18,19) and improved dental prosthodontics have revolutionised maxillofacial reconstruction. Following surgery, early wound closure and the restoration of form, cosmetics and function are the goals of reconstructive surgery (1,6). This article seeks to review the modern methods employed in the reconstruction and rehabilitation of the form and function of the jaws and mouth such as free tissue transfer, prostodontics and dental implants.

RECONSTRUCTION
Maxillofacial reconstruction is of prime importance in the management of orofacial defects caused by disorders such as neoplastic disease. The modern techniques for reconstruction are discussed below.

Vascularised Free Tissue Transfer
Vascularised free tissue transfer (VFTT), also known as free flap transfer, is now considered the gold standard for maxillofacial reconstruction (4,6). It involves the harvesting and detachment of tissue with it's blood and nerve supply and transferring it to repair a defect, where its blood and nerve supply are re-established by re-anastomosis to suitable recipient site vessels (6). Success rates are estimated at between 90% and 94% (20-22). VFTT is advantageous over non-vascularised transfer, as post-operative radiation affects the vascularied flap less severly compared to the non-vascularised flap due to the transferred blood supply. A number of different donor sites are used for VFTT, the selection of which depends on the recipient site and type of tissue being replaced (5-7,13,18,20-30). The principle types of flaps used in reconstruction are discussed below.

Fibula free flap is regarded as the mainstay in mandibular reconstruction (19,20,23,31). Long vascularised cortical bone is provided from the fibula and can restore angle to angle mandibular defects. The fibula allows placement of osseointegrated dental implants (19). Disadvantages include donor site morbidity and numbness of the foot and toe (32).

Radial forearm free flap is used mainly to restore lateral edentulous defects. The main disadvantages of this flap are inadequacy of available bone and donor site morbidity such as limited motion, grip strength and supination (4,32). Limited bone stock reduces the quality of osseointegration (19). Frodel et al. showed that the radial flap had the largest number of specimens with inadequate bone volume for implant placement (13). However the advantages of this flap are that it offers a sensate skin paddle for intra-oral reconstruction and allows a two-team operative approach (19). The risk of radial fracture is estimated to be 17% (23) and this flap is now regarded as less popular for mandibular reconstruction. However, it is useful when restoring the anterior maxilla and non-tooth bearing areas of the mandible (24) and when soft tissues need to be reconstructed.

Scapular free flap is an osteocutaneous flap and is a recommended choice for complex defects involving facial skin, bone and mucosa (25). This flap, in general, accepts osseointegrated dental implants well (19)and a study of 55 patients over twelve years showed a success rate of 89% (26).

Iliac crest free flap offers the best bone stock for dental implants (19). The natural contours of the bone are helpful for reconstructing lateral and hemimandiblectomy defects and studies show no significant differences in terms of orthopaedic or quality of life outcomes (27). The iliac crest has remained the reconstructive flap of choice in dentate patients (23) and the success rate in a recent review was found to average 96% (29).

REHABILITATION

Maxillofacial rehabilitation is the second important step in the management of patients with orofacial defects as it restores the function of the region. Several important modern methods are discussed below.

Prosthodontics

Prosthodontics (the replacement of missing teeth with artificial materials, such as a bridge or denture) is a treatment modality that depends on the degree of dentulousness (presence of teeth) or the type of defect present. A fixed prosthesis is a device, such as a bridge or denture, which is securely retained by natural teeth, teeth roots and/or dental implants. Fixed prostheses avoids pressure on the mucosa which may be tender, dry and friable in irradiated patients (32). Reports have shown that bone loss in the edentulous maxilla is greater when fixed prostheses are used in place of overdentures (33). A study by Watson et al. showed that overdentures involved more postoperative treatment than fixed prostheses for adjustments and mechanical problems (33). A recent consensus report stated that the implant-supported overdenture is the gold standard in restoring the edentulous mandible (34). In patients with dry mouth, secondary to radiotheraphy for oral SCC, serious concerns regarding ability to maintain oral hygiene must influence treatment options. Teeth with a poor prognosis should be extracted before radiotherapy to avoid osteoradionecrosis (30).

Dental Implants

Osseointegration, which is the basis of dental implants, has revolutionised the restoration of the oral cavity. The technique involves the direct attachment of osseous tissue to an inert, alloplastic material without intervening upon connective tissue. It has allowed increased denture retention and fixed placement of restorations in otherwise edentulous spaces but studies have shown that up to 6-7mm height of bone is required in order to carry out this technique (16). A study looking at the success rate of implants into 6mm of bone height showed that 10.7% failed (14), while the overall mean survival rate in fourteen trials with follow-up periods of 2-16 years involving 10,000 implants was found to be 94.4%, with a success rate 86.8% for grafted bone (15).

Implants placed in reconstructed bone perform identically to those placed in native bone and the quality of bone was found to be the greatest determinant of fixture loss (35). Patient satisfaction with this technique is high. In a study carried out on twenty-eight patients, 85% reported satisfaction with the implants in reconstructed jaws and had no social problems (17).

The use of implants in irradiated bone has been controversial. There is a risk of developing osteoradionecrosis of the mandibular bone when carrying out surgical procedures such as implant placement. In patients about to receive radiation post-operatively, implants should not be loaded for six months (7). The overall success rate for endosteal dental implants was 92%. The implant success rate was 86% when the bone, in which the fixtures were placed, was irradiated postoperatively. In the fourteen fixtures that were placed into previously irradiated bone the success rate was 64% (7). The greater success of native bone and vascularised bone flap osseointegration compared to free bone grafts has been noted (31).

Several factors need to be considered in implant placement in patients treated with radiation therapy for oral malignancies. The use of hyperbaric oxygen has been show to prevent osteoradionecrosis in patients undergoing post-radiation mandibular surgical procedures (30). The risk of osteoradionecrosis is dependant on the dose of radiation (30). Zygomatic implants are a useful treatment modality, where insufficient bone exists for maxillary implant placement. These factors are discussed in detail below.

Hyperbaric Oxygen Therapy (HBO): The vascular vessels in the field of irradiation are narrowed causing a decreased blood flow to the region. Irradiated host bone had been regarded as a contraindication to implant placement (28). HBO is used by some as a precaution before implant placement in irradiated bone to reduce the likelihood of osteonecrosis (36). However, studies have shown acceptable results in irradiated bone without HBO (37).

Radiation Dose: There has been some discussion in the literature as to the importance of radiation dose on implant survival, suggesting that an upper limit of 55 Gy (30) should not be breached without the use of HBO. Disagreement as to when implants should be placed in irradiated bone still remains (31).

Zygomatic Implants: Introduced by Brånemark in 1998, this long implant is used to restore atrophic posterior maxilla in maxillectomy patients and has a success rate of between 82 and 97% in oncology patients (8,38). Zygomatic implants may be an alternative procedure to bone augmentation and sinus lifts (8) but failure is more problematic than dental implants.

THE FUTURE ADVANCES OF REHABILITATION OF THE OROFACIAL REGION

Several advances that may in time have significant applications in the field of orofacial reconstruction are currently under investigation and are discussed below.

Scaffold Materials

In maxillofacial rehabilitation procedures, scaffold materials such as proceramics and polymers are becoming more commonplace to help rebuild the bone. Ceramics, such as hydroxyapatite and β-tricalcium phosphate, are strong enough scaffolds to provide mechanical strength when replacing load bearing skeletal structures (12). Polymers, such as polyglycolic and polylactic acid, are also used but lack mechanical strength and may cause uncontrolled shrinkage of bone (11). Currently available scaffold materials have a number of drawbacks such as insufficient penetration of cells and bone throughout the scaffold, inadequate degradation properties, or inadequate mechanical stiffness (11).

Growth Factors

Bone morphogenic proteins (BMPs) are growth factors and cytokines known for their ability to induce the formation of bone and cartilage (39). Basic fibroblast growth factor is considered to enhance angiogenesis and to support bone formation in the presence of vital bone cells (10). However, there is no reliable evidence supporting the efficacy of agents such as platelet-rich plasma in conjunction with dental implant therapy (3) or wound healing (40).

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Distraction Osteogenesis

Distraction osteogenesis (DO) has been used in correcting craniofacial deformities of the mandible allowing gradual deposition of bone where two segments of bone are moved apart from each other. In a study on the reconstructed mandible, an average gain of 11mm of bone length was achieved using DO (41). The procedure works well in oncology patients who experience poor functional outcomes after surgery due to scar formation or inadequate bone length (4), but comes with a higher risk of failure and complications (41). There is insufficient evidence as to whether DO is the best method available for vertical bone regeneration (3).

Alloplastic Materials

Alloplastic materials have been used successfully in the treatment of defects in conjunction with VFTT reconstruction (39). Titanium hollow screw osseointegrating reconstruction plates (THORP), which are rigid locking plates with osteosynthetic capacity, are used and they have a recorded hardware-related reconstructive failure incidence of only 7% when used with VFTT free flaps (6). Locking miniplates and double-threaded screws are the latest innovation, which allow the locking to both bone and plates to increase stability.

Rigid Fixation

The development of osteosynthesis plate technology has allowed biocompatible materials to internally fix fractures and unionise bone grafts with great success. Recently, biodegradable, self-reinforcing polylactide and polyglycolide plates/screws have been used for internal fixation of mandibular fractures with excellent success (2, 9). This technique allows accurate correction of fractures but being part of an invasive procedure is it's main drawback.

DISCUSSION

Reconstructive maxillofacial surgery can now draw upon many techniques in the reconstruction and rehabilitation of the orofacial region and reliable osseous reconstruction. Major institutions boast successful bony union rates of 95% (4, 42). In reconstruction, the choice of flap depends on the tissue type being replaced and the choice of donor site. It seems that non-vascularised tissue transfer is no longer the accepted first line treatment in orofacial defects and it is now superceded by vascularised tissue transfer. In the past, non-distant pedicles were used to restore maxillofacial defects, giving way in recent years to free flaps. Initial research has reported high levels of success with free flaps but data from randomised or comparative trials are needed to support this research (23).

From the review of the literature it seems that osseointegrated implants offer the best functional and aesthetic outcomes, achieving success rates up to 94%. However some papers have expressed caution about their use in irradiated patients (36,37). They are employed, not only to restore the dentition, but also to restore other anatomy such as the eye.

Advances in grafting and biomaterials have led to much success, not only in maxillofacial surgery but in periodontics and restorative dentistry. Sinus augmentation procedures allow implants to be placed in areas of bony atrophy. Bone substitutes may prove to be as effective as autogenous grafts for augmenting extremely atrophic maxillary sinuses. Upon healing, sites treated with xenografts (Bio-Oss) and barrier membranes show a higher position of the gingival margin compared to sites treated with barrier membranes alone (3).

Distraction osteogenesis and the use of growth factors such as BMPs have shown promise but further research needs to be undertaken before these modalities are recommendable. Much research is being carried out in the field of muscular and neural tissue regeneration and this may play a role in orofacial reconstruction in the future.

CONCLUSION

Orofacial defects can have detrimental functional and psychological effects on the patient. However, in the modern maxillofacial world, the surgeon has a wealth of techniques to draw upon to manage such defects. The management involves either surgical reconstruction or prosthetic rehabilitation or a combination of both. Microsurgery, osseointegration and bone technology have become the keystones in orofacial reconstruction and major advances in recent years have resulted in more treatment modalities and increased success. The future for maxillofacial reconstruction is bright as a wide range of techniques are being developed to improve upon the advances of the past few decades.

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Gene Polymorphisms in the Renin-Angiotensin-Aldosterone System and Breast Carcinogenesis: Is There a Connection?

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Clinical Points:

- A positive correlation may exist between polymorphisms of genes that code for proteins of the renin-angiotensin-aldosterone system and a risk of developing breast cancer. These genes code for angiotensin converting enzyme (ACE), angiotensin II receptor type 1 (AGTR1) and angiotensinogen (AGT).
- The polymorphisms in the ACE gene cause variations in the level of ACE and thus the level of angiontensin II in plasma. This increased level of angiotensin II is thought to be one of the determining factors in breast carcinogenesis and therefore long term use of ACE inhibitors in females may prove to be protective against breast cancer.
- The single nucleotide polymorphisms in the AGTR1 gene may reduce the risk of breast cancer by determining the binding efficiency of angiotensin II to the receptor. This receptor may provide a useful target for pharmacological therapy in patients suffering from breast cancer.
- In the future, polymorphisms in ACE, angiotensin II or AGT may prove to be markers for breast cancer.

ABSTRACT
Breast cancer is the second most common type of cancer in the world. In this article, studies are considered, which suggest a pattern may exist between polymorphisms in genes of the renin-angiotensin-aldosterone system (RAAS) and the risk of developing breast cancer. Polymorphisms of angiotensin converting enzyme (ACE), angiotensin II receptor type 1 (AGTR1) and angiotensinogen are investigated. The polymorphisms in the ACE gene cause variations in the level of ACE and therefore affect the level of angiontensin II, which is thought to contribute to breast carcinogenesis. Studies into insertion/ deletion (I/D) polymorphisms and the single nucleotide polymorphism (SNP) A-240T show that carriers of the DD genotype of the I/D polymorphism or the TT genotype of the SNP had significantly greater chances of developing breast cancer than carriers of the II or AA genotypes. SNPs in the AGTR1 gene may reduce the risk of breast cancer by either determining the binding efficiency of angiotensin II to the receptor or by interfering with the downstream signaling cascade that is required for angiotensin II to elucidate it's carcinogenic effect. Studies on the SNPs A-168G, C-535T and T-825A are presented here and it is evident that carriers of the AA genotype, CC genotype and TT genotype may have a higher risk of developing breast cancer than carriers of GG, TT and AA genotypes respectively. A SNP, M-235T, in the angiotensinogen gene also supports the connection of polymorphisms in the RAAS system to breast cancer. This receptor may provide a useful target for pharmacological therapy in patients suffering from breast cancer. In the future polymorphisms in ACE, angiotensin II and AGT may prove to be markers for and long term use of ACE inhibitors may prove to be protective against breast cancer.

INTRODUCTION

After lung cancer breast cancer is the second most common type of cancer worldwide (1) and the fifth most common cause of cancer death (2). Breast cancer is by far the most common cause of cancer incidence and death among women (2) with a global age adjusted incidence of 127.8 per 100,000 annually (3). Like other forms of cancer it is considered to be a multi-factorial event, with both environmental and hereditary factors contributing to the onset of the disease. Such factors include genetic mutations due to oestrogen levels (4), failure of immune surveillance (5) and inherited defects in DNA repair genes such as BRCA1 and BRCA2 (6).

Recent papers have suggested a connection between breast cancer and the renin-angiotensin-aldosterone system (RAAS) (7-10). RAAS is an endocrine system made up of interactions between the metabolites angiotensinogen, angiotensin I, II and III and angiotensin converting enzyme (ACE). This system plays a crucial biological role in the regulaton of vasoconstriction, Na^+ retention, aldosterone and anti-diuretic hormone release (11). The aim of this paper is to review the literature of studies carried out on particular polymorphisms of ACE, angiotensin receptor 1 (AGTR1) and angiotensinogen genes to determine whether a pattern exists between these polymorphisms and the risk of developing breast cancer.

Breast Cancer and the Pattern of ACE Gene Polymorphisms

ACE is a membrane bound dipeptidyl carboxypeptidase which converts angiotensin I to angiotensin II, and is the rate limiting step in the RAAS (11). Three investigators - Koh et al. (12), Ladd et al (13) and Haiman et al (14) - have looked at the patterns of two ACE gene polymorphisms and their possible connections to the risk of developing breast cancer (see Table 1.). The ACE polymorphisms examined were (i) an insertion/deletion (I/D) of a 287 base pair Alu-type sequence in intron 16 and (ii) a single nucleotide polymorphism (SNP) A-240T.

Koh et al., in the Singapore Chinese Health Study, found

Poymorphisms of the ACE gene	Chinese Health Study Koh et al.	Rotherdam Study Ladd et al.	Multi-Ethnic Cohort Study (USA) Haiman et al. Data on all groups
A-240T			
TT	↑↑	↑↑	↔
AT	↑	↑	↑↑
AA	↔	↔	↑
Insetion / Deletion			
DD	↑↑	↑↑	↔
ID	↑	↑	↑
II	↔	↔	↑↑

Table 1. Comparative summary of 3 studies that look at the pattern of polymorphisms found in the ACE gene and the risk of developing breast cancer. The two polymorphisms that were studied were a SNP A-240T and and I/D polymorphism of a 287 base pair Alu-type sequence. ↑↑ : high risk of breast cancer, ↑ : intermediate risk of breast cancer, ↔ : low risk of breast cancer.

that women carrying the polymorphism TT or DD had a significantly higher risk of developing breast cancer than those with the genotype AT or ID while the polymorphisms AA or II carry the lowest risk of breast cancer (12). This result was supported by the Rotterdam study, a case control study on 4,117 women in Holland (13). Ladd et al. found that DD carriers showed a significantly increased risk of developing breast cancer compared to II carriers, an observation that remained even after adjusting for other risk factors such as BMI, age at menarche and menopause and hypertension (see Table. 1). Cancer free survival was also significantly reduced in carriers of the DD polymorphism compared to those with the II polymorphism (13). These studies strongly suggest a link between these polymorphisms and breast cancer. However, Haiman et al in a multiethnic cohort study found conflicting results and concluded that the SNP A-240T and the I/D ACE polymorphisms are not strong predictors of breast cancer risk (see Table 1)(14). When all three studies are considered the results from Koh and Ladd are the most statistically significant. Also the Rotterdam study has the largest sample size and so the evidence is thus in favour of ACE polymorphisms leading to an increase in the risk of breast cancer.

Breast cancer and the pattern of AGTR1 gene polymorphisms

Angiotensin II elicits an effect by binding to both AGTR1 and AGTR2 (7,15). Binding of angiotensin II to AGTR1 stimulates angioneogensis, cell growth and cell proliferation (8,16) while bindingof angiotensin II to AGTR2 causes growth inhibition and cell apoptosis (8,17,18,19). Therefore the effect of angiotensin II on apoptosis depends on the balance of expression of the two receptors on the cell membrane. Increased AGTR1 coupled with decreased AGTR2 expression is observed in breast carcinoma (7,9), laryngeal carcinoma (20), and also squamous cell carcinoma (21) which suggests that its over expression is associated with carcinogenesis.

A follow up study on the Singapore Chinese health study examined the pattern of a number of SNPs in the AGTR1 gene, A-168G, C-535T, T-825A and their connection to breast cancer (22). This study found that the high risk genotypes for breast cancer include the homozygous

SNPs in AGTR1 Gene	Risk of Breast Cancer
A-168G	
AA	↑↑
AG	↑
GG	↔
C-535T	
CC	↑↑
CT	↑
TT	↔
T-825A	
TT	↑↑
TA	↑
AA	↔

Table 2. An overview of three SNPs of the AGTR1 gene and the risk of developing breast cancer. ↑↑ : high risk, ↑ : intermediate risk, ↔ : low risk

alleles AA, CC and TT (see Table 2.). It was also found that the risk of breast cancer was significantly reduced in women who were carriers of the intermediate or low risk SNPs; with an Odds Ratio (OR) of 0.84 (95% confidence intervals (CI) = 0.51-1.37) for women possessing one low risk SNP and an OR of 0.68 (95% CI = 0.46-1.01) for women possessing two/three low risk SNPs (22).

An interesting finding in this study was the additive effect in the reduction of risk of breast cancer that was observed when polymorphisms for both ACE and AGTR1 were considered (see Table 3.). Women possessing the low risk polymorphisms of AGTR1 and ACE had an OR of 0.35 (95% CI = 0.20 – 0.62) of breast cancer risk. This is significantly lower than the breast cancer risk in women who possess only one of these poymorphisms. This observation lends further weight to the argument that gene variations within the RAAS may play a role in breast carcinogeneis.

Breast Cancer and the Pattern of Angiotensinogen Gene Polymorphisms

Angiotensinogen is the precursor of angiotensin I in RAAS.

AGT1R Poylmorphisms	ACE Polymorphisms High Risk	Low Risk
	OR (95% CI)	OR (95% CI)
High risk	1	0.46 (0.28 – 0.76)
Low risk	0.57 (0.25 – 1.32)	0.35 (0.20 – 0.62)

Table 3. An overview of the high or low risk combinations of AGT1R and ACE polymorphisms and their risk of developing breast cancer. OR=odds ratio, CI = confidence interval.

Ladd et al. investigated a possible link between the pattern of the SNP, M-235T, in the angiotensinogen gene and breast cancer risk in caucasian postmenopausal women and found that women carrying the MM genotype were more likely to have breast cancer in comparison to the MT and TT genotypes (see Table 4.) (23).

SNP in Angiotensinogen gene	Risk of Breast Cancer
M-235T	
MM	↑↑
MT	↑
TT	↔

Table 4. An overview of the variable AGT polymorphisms and the risk of developing breast cancer. ↑↑ : high risk of breast cancer, ↑ : intermediate risk of breast cancer, ↔ : low risk of breast cancer.

DISCUSSION

Polymorphisms in the the RAAS system have an established association with cardiac disease (11). In this review, we were interested in examining the possible link between gene polymorphisms in three proteins of the RAAS system, ACE, AGTR1 and angiotensinogen and breast cancer. The review of literature suggests a positive correlation exists between polymorphisims in these genes and a risk of breast cancer but one must wonder by what mechanism do these polymorphisms result in the development of breast cancer and what are the future implications of such a connection?

1) How do polymorphisims in ACE lead to an increase in breast cancer risk?

According to the studies carried out by Koh et al (12) and Ladd et al (13) both polymorphisms of ACE, the insertion or deletion of a 287 base pair Alu-type sequence and an A-240T SNP, may lead to an increased risk of breast cancer by affecting the level of ACE produced *in vivo*. If ACE is increased in the plasma there is an increase in the production of angiotensin II which is thought to be the direct cause of breast cancer via the binding to its receptors AGTR1 and AGTR2.

Studies into the ACE levels in plasma have shown that they vary between 28 and 47% depending upon the insertion or deletion of the Alu-type sequence (12,24,25). The SNP A-240T also results in variations of ACE levels in the plasma, with the homozgous genotype TT resulting in the highest level of ACE, the homozygous genotype AA resulting in the lowest level of ACE and the TA genotype resulting in levels of an intermediate level. These patterns of fluctuating ACE levels are consistent with the prevalence of breast cancer risk.

Haiman et al. (14) in their multiethnic cohort study concluded that A-240T and I/D ACE polymorphisms are not likely to be strong predictors of breast cancer risk (see Table 1.). However, this finding may be due to the fact that it was a US based study and it is well recognised that the effect of a given gene on disease risk is masked in racially mixed populations (26,27). The studies of Koh et al. and Ladd et al. were performed in Singapore and the Netherlands respectively, countries which have much more homogenous populations than the US and therefore would not have had the risk of masking of the genetic effect on the disease. Diet derived long chain polyunsaturated fatty acids and tea polyphenols have been shown to modulate the effects of angiotensin II on the cardiovascular system (22) and Koh et al used this observation to offer another explanation for the conflicting data of the Haiman et al. study when they pointed out that differences in diet, especially between the populations in Singapore and the US, may exert an influence on the effect of angiotensin II on breast carcinogenesis.

2) How do polymorphisims in AGTR1 lead to an increase in breast cancer risk?

Angiotensin II appears to exert a carcinogenic effect via the AGTR1 receptor via three different pathways by: i) inducing cell division via regulation of mitogenic signalling pathways achieved by transactivation of protein kinase C and epidermal growth factor receptor (28), ii) angioneogenesis and promoting arterial smooth muscle cell proliferation via vascular endothelial growth factor from nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (8,16,29) and iii) production of reactive oxygen species from NADPH oxidase (30,31)

The SNPs A-168G, C-535T, T-825A all decreased the risk of breast cancer (22) which suggests that a variation in the receptor AGTR1 does not allow angiotensin to bind correctly and initiate the carcinogenic intracellular signaling pathway. It was also found that those people who had the combined low risk genotypes of AGTR1 and ACE had an even lower risk of breast cancer when compared to carriers of only one. Further evidence that angiotensin II binding to AGT1R is involved in breast cancer has been the observation losartan prevents the proliferative effects of angiotensin II in vitro and in animal models (7,28).

3) How do polymorphisims in AGT lead to an increase in breast cancer risk?

It is important to point out that the study of genetic polymorphisms in AGT is not as straightforward as the study of genetic polymorphisms in ACE or AGTR1. While an increase in AGT does lead to an increased level of angtiotensin II which is thought to be a carcinogenic factor, AGT does have antiangiogenic actions such as reducing endothelial cell proliferation and migration (32). Ladd et al. found that women carrying the MM genotype of the M235T AGT polymorphism had an increased risk of developing

breast cancer when compared to those women carrying the MT and TT genotypes. The authors felt that the findings suggested that the antiproliferative effects of AGT may override the proliferative effects of angiotensin II. It is important to note that the conclusion of the above study is controversial and further studies on the subject are required before any firm conclusions may be drawn.

4) The Future - ACE inhibitors in breast cancer ?

If a connection is established between genetic polymorphisms in the ACE gene, ACE plasma levels and the risk of breast cancer, then it may be possible to use ACE-inhibitors (ACE-I) not only as an antihypertensive but also as an anti-carcinogenic therapy. Lever et al. created much excitement with their paper when they found that hypertensive patients on ACE-I had a lower risk of cancer versus population controls, the lowest being breast cancer (10). Other antihypertensive treatments had no apparent effect on risk of cancer and the authors concluded that long-term use of ACE-I may have protective properties against cancer. However numerous negative studies such as the one from Fryzek et al. do raise a significant point that the prevention of breast carcinogenesis with ACE-I may only be beneficial in patients with an increased genetic expression of ACE and AGT1R levels (33). While not suggesting that ACE-I should be given prophylactically to prevent breast cancer, it may be viewed favourably when choosing a class of antihypertensive medication. The relationship may indeed be likened to the protective role of low dose aspirin and colorectal carcinoma. The new knowledge of these potential benefits of ACE-I in breast cancer coupled together with their known potency in lowering morbidity and mortality in hypertension helps to strongly suggest ACE-I as a first line treatment in hypertensive individuals and perhaps more so in women.

CONCLUSION

Polymorphisms in the genes encoding proteins of the RAAS system examined ie. ACE, AGTR1 and AGT, may play an important role in determining the risk of breast cancer. It is thought that these polymorphisms may provide markers for breast cancer in the future, although more detailed trials and experiments are required to confirm this conclusion. Also, it may be possible that pharmacological inhibition of the angiotensin II carcinogenic effect, by inhibition of either ACE or AGTR1, could be used to prevent or treat breast cancer.

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One Small Step or One Giant Leap Towards Access to Medicines For All

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ABSTRACT

In December 2005, the World Trade Organisation members amended the Trade Related Aspects of Intellectual Property Rights agreement to find a solution to the problem of access to medicine. However, intellectual property provisions, as delineated in bilateral and regional free trade agreements, have the potential to undermine their purpose and success.

INTRODUCTION

A land mark in the fight for availability of generic medicines in developing countries was arrived at in November 2007. The European Union (EU), announced it had formally accepted the World Trade Organization (WTO) approved protocol of 2005, amending the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement. The amendment makes permanent a temporary waiver of the Doha Agreement of 2001, allowing for drugs produced under compulsory licence to be predominantly for the supply of the domestic market. However, in order for the decision to have legal effect, two-thirds of the 151 WTO members are required to ratify the agreement. EU acceptance only brings the number to 41[a]. With so many obstacles one must wonder if universal access to medicines a realistic goal?

The rules of TRIP govern the proprietary interests in ideas, processes and products, and how the protective measures encompassed in these rights may be penetrated in the event of a "national emergency". The Doha Declaration of 2001 reaffirmed the flexibilities available within TRIPS, and asserted that the agreement should be interpreted in a manner that protects and promotes access to medicines and public health. Doha later led to the agreements of 2003 and 2005, which represented other stepping stones in the fight for availability of generic medicines in developing countries. This article considers the applicability of the 2005 agreement and how recent US free trade agreements (FTAs) are now compromising its potential.

GENERIC MEDICINES

Currently 33.2 million people worldwide are living with Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS). Of these, over 31.3 million live in developing countries, with two-thirds in sub-Saharan Africa (2). A number of academic commentators attribute the problem to the apathy of most Western countries (3). While HIV/AIDS crosses national and class boundaries, it is not an epidemic here in Europe as it is in Africa. The public may well be aware of this problem, but few are affected by it on a daily basis. Therefore, the issue becomes sidelined and the lacklustre response from the developed world means that developing countries must address their needs themselves but they often encounter difficulties with patenting laws and subsequent threat of litigation. The availability of generic drugs is the only manner in which developing countries can begin to tackle this growing problem.

Pharmaceutical Research and Manufacturers of America (PhRMA) argues that adequate patent protection should be afforded to encourage investment in Research & Development (R&D) and that a failure to give adequate patent protection results in a disincentive to invest in this important area. While the author agrees that inventiveness should be rewarded, the author submits many policy arguments advocating the development of the generic pharmaceutical industry. One such argument is that R&D may take many years and this is reflected in the price of on-patent drugs. A number of fundamental issues arise in justifying on-patent drugs for immediate crises as long-term R&D is redundant when people are dying (4). For those diseases which are not immediately threatening, few in developing countries can afford to pay for the on-patent drug. The crude reality is that for many illnesses affecting developing countries, there is no R&D by pharmaceutical companies. Companies will not invest in such drugs when patients cannot pay for them. The flexibilities developed and interpreted in TRIPS therefore represent an effective solution in promoting access to essential medicines.

PATENTS AND LICENCING

The Doha Declaration in 2001 catalysed a number of subsequent agreements on the provisions of TRIPS and their potential to fulfil the agenda of access to medicines for all. Essentially a number of "flexibilities" are contained within the agreement. For example, member states are protected against anti-competitive practices and patents may be used without permission in limited circumstances.

The Doha Declaration arose as an interpretative tool in the analysis of TRIPS, which states that compulsory licensing shall be "predominantly for the supply of the domestic market". Basically, the majority of developing countries do not have the available resources to develop on-patent pharmaceuticals locally. The reinterpretation thus represents a means of ensuring access to essential medicines in developing countries. In 2003, a temporary waiver was issued allowing for the issuance of compulsory licences. Countries without the requisite manufacturing capability were permitted to import drugs from countries with local manufacturing capacity. This was based on the caveat that exporting countries would not use the

a Delineated in Paragraph 4 of Doha Declaration.

Declaration "...to pursue industrial or commercial policy objectives." Poorly developed countries or those countries capable of proving an absence of manufacturing capability could avail of the provision.

The implementation of the Doha Declaration represents a means for developing countries to address their public health problems as it provides flexibility by granting number of other options: compulsory licensing, the use of parallel importation, and the development of generic medicines to combat HIV/AIDS, malaria, and tuberculosis. In July 2007, Rwanda informed the WTO that it was availing of the Declaration to import cheaper generics made under compulsory licensing elsewhere and thereby became the first country to avail of this provision.

POTENTIAL PROBLEMS

A number of potential problems arise in attempts to implement the Doha Declaration. In addition to economic and political challenges, there are also substantial administrative burdens, which Professor Brook Baker regarded as “cumbersome” and a “procedural labyrinth.” First, in the case of compulsory licences, both importing and exporting countries must issue licences. The compulsory licence issued by the exporting country is based on a “single-supply basis,” hence this process must be repeated for each request. Secondly, a developing country must prove insufficient or no local manufacturing capacity in order to qualify. Finally, notice must be given to the WTO of the intention to use particular products, the quantities of such products, and the particular country’s lack of adequate manufacturing capacity. Although the administrative requirements on drug-by-drug, country-by-country basis are not insurmountable, they do represent a further obstacle to acquiring good quality generic pharmaceuticals.

Parallel importation can give rise to defective and second-rate products arriving on the market. The agreement lays down requirements for those countries importing the goods to take “reasonable steps” in preventing the re-exportation of the goods, in particular labelling and marking of the product. This incurs an additional expense inevitably borne by the importing country. Countries exporting drugs under this provision will also need to satisfy strict administrative requirements. Correa has argued that administrative requirements specifying that low-priced medicines cannot be produced because "...meaningful economies of scale have not been reached..." results in a failure "to promote access to medicines for all" (5).

Amir Attaran and Lee Gillespie-White argue that patents themselves are not a barrier in the access to antiretroviral drugs in Africa (3). They state that poverty, lack of international funding, and limited donor spending represent more significant barriers. Essentially, they concluded that few patents existed in South Africa at the time and that "geographic patent coverage [did] not appear to correlate with antiretroviral treatment access." Attaran and Gillespie-White blame the lack of international aid for maintaining the status quo. Non-Governmental Organisations disagree with the contentions of Attaran and Gillespe-White and argue that the most fundamental patents have been strategically patented by pharmaceuticals, and those which are unpatented remain so as they would not aid in community development [b]. The fact that other antiretroviral drugs may exist off-patent is of little practical value if the majority of patients are using a particular “in use” antiretroviral drug.

The developing world makes up 80% of the world’s population yet accounts for only 20% of its uptake of pharmaceutical goods. Helena Vines Fiestas, author of a recent Oxfam report, confirms, “High levels of intellectual property protection have not resulted in new cures for diseases that affect poor people,” and further cites a United Nations estimate that nearly 2 million people in developing countries are denied access to essential medicines (6).

Patents invariably pose a great obstacle for those seeking treatment, as patented drugs are outside their price bracket. Attaran (7) explains that in 65 low and middle income countries the level of patenting for products is very low averaging only 1.4 patents per country. However, the drugs that are on patent are the most practical and effective regarding income and infrastructure in these countries. In comparison, the off-patent drugs are more expensive and difficult to administer and are thus not desirable to suffering patients. These results highlight the policy arguments regarding the corporate structure and access to essential medicines

Cohen et al. (8) in a recent paper examined the current state of affairs in Ghana. Through his compilation of information, we learn that in real terms the treatment of HIV/AIDS would require someone working on a minimum wage 5 days to cover the cost of treatment. Yet to add to this, many patients are unemployed and thus are unable to afford this treatment. The availability of generic drugs is thus a viable solution.

A further question arises as to why so few countries have aligned themselves with the waiver on licensing. While protective measures for developing countries are present in the TRIPS agreement, a fear exists that governments may be wary of using such measures for fear of political ramifications. In April 2007, the Thai government announced it would issue compulsory licences to manufacture low-cost versions of the non-nucleoside reverse transcriptase inhibitor efavirenz, the second-line combination anti retro viral drug lopinavir/ritonavir, and the antiplatelet clopidpgrel. Abbott, who produces but lopinavir/ritonavir and clopidogel has now withdrawn all its future products from the Thai market. Following the Thai example, Brazil in July 2007 issued a compulsory licence and will now import a cheaper, generic Indian-made version

b On analysis certain flaws become evident in their study – it fails to take into account income levels, the rates of infection and the usage of the drug in question. A fundamental issue arises in that if the majority of on patent pharmaceuticals exist in countries with the highest levels of HIV/AIDS then these patents represent a barrier to the treatment of victims.

of the patented efavirenz drug. In the face of threats from drug companies, such moves are an exemplary beacon if universal access is to be obtained.

DATA EXCLUSIVITY & FREE TRADE AGREEMENTS

The EU position on data exclusivity is compliant with TRIPS[c]. Essentially the first person to manufacture a product must submit evidence as to its safety and effectiveness. A subsequent generic manufacturer who wishes to bring the same drug to the market does not need to repeat the experiments once they show that the drug is of the same quality as the original drug. This allows the drug to come on the market quickly and at low cost due to the absence of an accumulation of clinical trails data.

While TRIPS allows for the protection of undisclosed clinical test data from "unfair commercial use" [c], no period of data exclusivity is specified, and the act does not specify that the original applicant have a period of data exclusivity. However, recent US bilateral and multilateral agreements are resulting in onerous TRIPS-plus requirements. The US free-trade agreements (FTA) effectively prevent generic manufacturers from using the original data to establish the safety and effectiveness of the drug. The FTAs refer to "HIV/AIDS, tuberculosis, malaria and other epidemics" and reflects the wording in Doha (9). Generic manufactures must either wait a further five years, allowing technically five additional monopoly years for the patent holder, or engage in tests of their own which are cripplingly expensive. This represents a formidable obstacle to compulsory licences and allows the rights holder to prevent a state from using such information for a period of five to ten years.

The provisions of the US FTAs effectively prohibit actions that are permitted under TRIPS and undermine the Doha Declaration. Both the US and EU are aiming for a de facto right for clinical trail data relating to new pharmaceutical products [d]. By bestowing exclusive rights on clinical trial results, the flexibilities of TRIPS become compromised. The use of original test data in clinical trials saves generic drug manufacturers considerable time and enables them to introduce the generic drug at a low price. The process of obtaining trial data would incur an additional expense on the drug. Essentially if the regulatory authority is unable to register a generic drug until the patent has expired, the compulsory licence is effectively redundant. It is prudent to note that if developing countries oppose these clauses seeking de facto rights for data, they may not gain favourable trade concessions from the EU and US. Professor Mercurio notes, "Many developing countries do not hesitate to trade off Intellectual Property Rights in exchange for market access" (10). He also adds that this is, in fact, the choice of developing nations and not the trading nation as one might expect.

Perhaps there is some merit in the argument for data exclusivity rights? The information generated by the original investor involves considerable time and skill and is a substantial investment, and therefore it is one which should be protected. The volume of data required in the approval of a new drug is immense, and exhaustive information is required before a drug will be given approval. Regulatory approval can take 8-12 years to complete and can involve €800m. From 5,000 potential molecules, only one will become a marketable pharmaceutical. Invariably generic companies do not wish to engage in this costly R&D as this involves a large amount of time and money (11). However, from the perspective of developing countries, a restriction on the use of data represents a significant hurdle in the use of compulsory licences; yet, as Professor Mercurio notes, developing countries continue to negotiate FTAs as bilateral agreements with trading nations which can provide concrete gains (10). For developing countries, the provisions of bilateral and regional trade agreements significantly delay the registration of a generic drug even if a compulsory licence has been issued. Thus, if access to medicines is to succeed, WTO members must ensure that the restriction on data does not apply to compulsory licences. The US argue that this is their interpretation[d] but essentially it results in an onerous TRIPS-plus standard on developing countries which have not achieved a level of development like that of the US [e].

A number of problems [f] exist with regard to the US position (12). Although the US has argued that side letters to the FTA contain waivers in the event of national emergencies, these carry little legal weight. The side letters effectively contradict the FTAs and are effectively subordinate to such. The reference to particular diseases intimates that certain public health issues may not be covered. Disconcerting is the reference to "necessity," a term rigidly defined in international law such that a country take only those steps "necessary". Necessity indicates the least obtrusive option or where there is no alternative. Inevitably such speculative legal standing is deterring for generic companies.

BOLD MOVES TOWARDS UNIVERSAL ACCESS?

A number of factors may prevent universal access to medicines. PhRMA has erroneously argued that Brazil and Thailand are too rich to issue compulsory licences. There is also a danger that weaker, more vulnerable countries may not follow the lead of Brazil and Thailand particularly when pharmaceutical giants like Abbott are threatening to withdraw life-saving medicines from those countries that dare issue compulsory licenses [g].

c In regard to Article 39.3 of TRIPS.

d The US has sought to use bilateral agreements with its FTA partners as a means of enhancing IP rights. These TRIPS plus provisions appearing in the free trade agreements of the US mirror US domestic law.

e Similarly Russia has consented to onerous FTAs focusing on the enforcement of IPRs in order to join the WTO. In doing so Russia has succumbed to US demands and the IP standards surpass the WTO agreement on TRIPS. Particularly onerous are provisions regarding compulsory licences for essential medicines and is another example of the US persistence on the matter.

f Not content with FTAs, the US responded to the Thai TRIPS compliant licence by placing it on the Special 301 Priority Watch-List.

g Another factor weighing against universal access is that the international TRIPS framework has finally been implemented in India resulting in even more difficulty in sourcing post-1995 medicines. Due to the "mail box" system in operation in India the number of on-patent drugs is set to increase.

Solace can be found in the synergy between the Clinton Foundation HIV/AIDS Initiative's work with generic companies, UNITAID's funds and expertise, combined with the World Health Organization (WHO) pre-qualification service. The Clinton Foundation has been greatly aided by UNITAID's purchasing power sourced from a new airline tax initiative which has resulted in a straightforward acquisition of second-line medicines (13). National drug regulatory authorities can permit fast-track registration of medicines as a result of a pre-qualification service with the WHO, while UNITAID are proposing collective management of intellectual property rights through patent pools encompassing patents and registration of data rights. Furthermore, an intergovernmental working group has also been set up by the WHO to deal with public health and innovation and will present their findings in 2008.

An additional positive step is a response to complaints by Democrats in the US. A template was suggested in May 2007. It is proposed that generic drugs will come to market quicker through trade agreements with trading partners. The approach suggests protecting pharmaceutical test data in partner countries for as long as it is protected in the US, but no longer — thus allowing generics to come to market in both countries simultaneously. A public health exemption is also suggested to temper data exclusivity obligations. Further proposals aim to approve generics with no pre-requirement of non-violation of a patent. Finally and perhaps most significantly is a proposal for side letters on public health to have a formal legal basis within the FTA structure.

CONCLUSION

If the problem of access to medicines is to be tackled effectively, compulsory licences must be excluded from the remit of data exclusivity. The burdens of bilateral agreements serve as additional weight that undermines the TRIPS agreement and the potential of the Doha Declaration. International aid, combined with an increase in local technical expertise provided through developed nations, is necessary for developing countries to understand the flexibilities of TRIPS and how it can use these to tackle access to essential medicines. The words of Professor Frederick Abbott ring true: "The political will of governments as well as the private sector is essential to determining whether or not matters are effectively addressed….If the government and its private sector are not committed, very little may be possible" (14).

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The Impact of Poverty on Health: A Fourth Year Medical Elective in Malawi

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INTRODUCTION

Set amidst the striking, mist-shrouded Mulanje Mountain Range, Phalombe, a small town in Southern Malawi, was home to four Trinity College medical students in July 2007. Having heard wonderful stories from our friends who had been there the previous year, we decided to make Holy Family Mission Hospital the destination for our four-week medical elective. Malawi is one of the poorest countries in the world and, as one can imagine, my experiences at Holy Family were quite different to anything I'd witnessed in any Irish hospital. Most startling was the very high case fatality rate and it wasn't long before I appreciated just how devastating absolute poverty can be in terms of health and disease. Phalmobe is located in a very poor and remote area that falls victim to many food shortages. Malnutrition, poor sanitation and lack of education in this region which are directly caused by poverty lead to poor health and disease.

In addition to my experiences at Holy Family, I was also fortunate to see the workings of the Likulezi Project, a local charity in Phalombe that was founded in 1993 in response to the devastation caused by the acquired immunodeficiency syndrome (AIDS) epidemic. Unsurprisingly for an area of such poverty, the adult human immunodeficiency virus (HIV) prevalence stands at 19%, much higher than the 10% seen in northern and central regions of Malawi (1). The project now plays an important role not only in combating AIDS, but also in helping combat poverty by supporting local enterprise and adult education. My experiences at Holy Family and the Likulezi Project allowed me to witness first hand just how important social and economic factors are in determining health. Previously I had given very little consideration to this crucial aspect of medicine and so, in this manner, my elective experience gave me a much deeper insight into the many factors involved in delivering effective health care.

HOLY FAMILY MISSION HOSPITAL

Holy Family is a 216 bed general hospital situated in the grounds of the Phalombe Catholic Mission, which is also home to a church, a convent and a large nursing school. The hospital has five main wards (male, female, paediatric, labour, and post-natal) and an outpatient's department. During our four weeks, we rotated through each of these areas and so were exposed to a very wide range of medical conditions. With only the most basic investigations available, well developed clinical skills are paramount, however with severe shortages of adequately trained staff this is difficult to achieve. Such limited resources mean it is also necessary to question the value and consequences of any investigation or intervention.

Lack of technology is not the only impediment to healthcare workers in the developing world. One of the innate difficulties faced by many health care facilities is earning the respect of local people. For many in Malawi, the witch doctor is the first port of call in times of sickness with the local health centre taking second place. As a result, many patients present to the hospital after their illness has progressed to a late stage. I believe that this reluctance to trust in basic Western health care stems from a lack of formal education. My experiences at Holy Family highlighted how education and promotion of health plays a crucial role in preventing disease.

MATERNAL MORTALITY AT HOLY FAMILY

In Malawi there are more than 1,000 maternal deaths for every 100,000 births, which is over 100 times greater than the Irish maternal mortality ratio (2). Out of 1,776 deliveries at Holy Family in 2006, 21 women died either during labour or in the peri-natal period. A ruptured uterus is the most common cause of maternal death in Holy Family which is usually caused by prolonged labour or multiparity (3). Grand multiparity is very common in Malawi and the fertility rate was recorded as 5.9 in 2005 (2).

Another obstetric complication common in this area of Malawi is cephalo-pelvic disproportion (3). Dr Anten, the Chief Medical Officer at Holy Family, attributed this to the very young age of most primigravidas and poor nutritional status during growth and development that results in women having a small, under-developed pelvis. In Malawi, there is a huge cultural pressure on women to bear many children. However, health promotion and education in the area of family planning could have a huge impact in changing reproductive choices and thus reducing maternal mortality. During my four weeks at the hospital, I witnessed only one bilateral tubal ligation. Perhaps not so surprisingly, the patient was a relative of one of the medical officers and so was probably very aware of the advantages of family planning.

INFANT MORTALITY AT HOLY FAMILY

In 2002 Malawi ranked 17th in the world for infant mortality with a rate of 113 per 1,000 live births. Maternal education is thought to be the most influential protective factor against infant mortality in Malawi (2). Although the paediatric ward in Holy Family had its own oxygen concentrator, many parents refused oxygen therapy for their children because they believed that it might harm them. This is an example of the many beliefs that are held by some people who have had very little formal education. During my four-week elective, two infants died from cardio-respiratory arrest secondary to severe respiratory distress caused by a lower respiratory tract infection. In both cases the parents had refused oxygen therapy for their children. I remember asking one of the clinical officers why they would not give the oxygen without the parents' consent, but I soon began to see how fruitless this would have been and how

damaging it would have been to the little respect that people had for western style medicine. The answer to this problem lies with education.

Lack of education is not the only obstacle of a functioning health care system in Malawi. For many people the mere act of getting to the hospital is momentous in itself. The hospital had a very high paediatric case fatality rate of 10.4% (3). Dr Anten cites “late presentation” to the hospital as the main reason for this. Holy Family is a private hospital and in order for patients to qualify for free health care they must be referred from their local District Health Office. Some of the referral centres are far as seventy kilometres from the hospital while transport is difficult to come by. In Phalombe, there was one village ambulance, which was a bicycle with a plank of wood tied to the back. Also the loss of income for a mother as many women, with many mouths to feed, cannot afford to stay in hospital with their sick children.

HOLY FAMILY HOSPITAL; CHALLENGES AND STRENGTHS

Notwithstanding the many barriers faced by people accessing healthcare, the actual service that the hospital can provide is constrained by extremely limited resources. For example, the hospital struggles to provide basic life support, as it has to contend with severe staff shortages and frequent stock outs of essential drugs such as local anaesthetic, antibiotics and even intravenous fluids.

Howver despite all of these problems there are many success stories. Holy Family is a designated Voluntary Testing and Counselling (VCT) Centre. This is the most common way people in Malawi and many places in Sub Saharan Africa get tested for HIV. VCT involves two counselling sessions; one given prior to testing andgiven post results. Patients are counselled about the virus, how it is spread and how to minimise the risk of infection. The VCT centre at Holy Family has five members of staff working voluntarily as part-time counsellors. In 2007, 4,093 people were tested and 34% of these were found to be HIV positive (3). This vast test number could not have been achieved without the selfless enthusiasm and dedication of the staff members who run the centre.

In Malawi, anyone with stage three or four AIDS is entitled to free treatment and Holy Family Mission Hospital also has an anti-retroviral (ARV) clinic, which was established in June 2005. The laboratory at Holy Family does not have the facilities to measure CD4 level, so clinical features are used to determine stage. By June 2007 there were over one thousand patients receiving ARV therapy through Holy Family (3).

THE LIKULEZI PROJECT

Gemma Brugha, an Irish nurse, who first came to Malawi in the 1980’s as a volunteer in Holy Family Mission Hospital, founded this local charity. Brugha has developed Likulezi into a sustainable, self-contained project because her experiences working in the hospital have taught her how disruptive outside influences can be. When she started working in Holy Family there were many foreign aid workers and volunteers in the area. At that time, the hospital was considered one of the finest in Malawi. However, after 1995, as the situation in Mozambique improved and the United Nations left, there was a mass exodus of foreign volunteers from the area. This sudden loss of staff and income had a disastrous effect on the hospital and wider community. Currently the project operates throughout three hundred and thirty villages and has over one thousand volunteers, all of who are Malawian (4).

The Likulezi Project plays a crucial role in the economic and social development of the community in Phalombe by operating in four core areas: AIDS education, home care and counselling for those with AIDS, orphan support and community development. I was fortunate to experience the workings of two aspects of the Likulezi project- home care and orphan support.

HOME CARE AND COUNSELLING

Home care plays a central role in the initial aim of the project which was to help alleviate the devastation and suffering caused by AIDS. Likulezi volunteers are trained not only as carers, but also as educators and so they encourage family members of the patient to get tested and counsel them regarding how to minimise the risk of infection. The project also provides these families with practical items, such as a bamboo mat to sleep on, soap, blankets and likhuni phala (a nutritious porridge). In visiting families out in remote villages with the volunteers, I got a real insight into the scourge that is HIV and how it devastates whole families and communities. The taboo and stigma associated with AIDS was evident as many people expressed their wishes not to talk about the disease especially in front of their children. There were also many patients with end stage AIDS who were unable to receive ARV therapy because they refused HIV testing.

THE LIKULEZI ORPHAN SCHEME

In 2005, it was estimated that there were over 800,000 orphans in Malawi (1). With no parents to support them, these children are forced to leave school at a very young age and find work in order to feed themselves and their younger siblings. The Likulezi orphan scheme aims to break this vicious cycle of poverty by supporting orphans and their families. In Malawi, the grandparents are frequently left to rear these orphans. Considering the prevalence of HIV in women between the ages of 20 and 24 is four times that in men of the same age (1), it is unsurprising that many AIDS deaths are in young mothers. One of the Likulezi volunteers and I visited an orphan family where the grandmother was taking care of three young children that had lost both parents. The mother had died of AIDS and as the father had abandoned his family once his wife became ill. We sat together on the bamboo mat provided by the project and listened to this old woman tell us of how she had to work as a labourer on other people’s land in order to make enough money to feed the children. However, the project had helped this family by supplying seed and fertiliser and supporting the orphans through

school. This support is given for a five-year period, after which the families can be included in a special revolving fund, where they are given a small amount of capital to make an income generating activity of their choice. One of the most important aims of the scheme is to keep the children in school and this is paramount in helping the community achieve long-term economic development.

LEARNING FROM EACH OTHER

The main lesson I took home from my four weeks in Malawi was how social problems strongly impact on health. I came across so many inspirational people that left me in no doubt that Malawi could overcome the many problems it faces. I found it remarkable how happy and generous ordinary people were. One evening when the four of us decided to go for a walk to the village we came upon an entire family, including grandparents and grandchildren, outside their small house singing and dancing. We stood there, captivated by their beautiful, harmonious singing and I remember thinking how wonderful it was that people can be so content and happy, despite their many struggles.

I met many remarkable people during my four-week elective but I particularly remember one of the volunteers from the project. One hot afternoon, the four of us cycled with her to a small village about twenty kilometres away where she helped care for a young mother who was dying of AIDS. This volunteer herself looked worryingly thin and she carried her two-year-old son on her back while she cycled. This was a woman who probably struggled to feed her own family, who could well have had grave health problems of her own and yet she was taking time to try and help another woman and her family. This is the lasting image that returns to me when I reminisce about my summer in Malaw. Malawi may have a lot of progress to make in several areas, such as education and health but there are also many lessons our society could learn from the people of this beautiful place.

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Past TSMJ Directors and Chief Editors

YEAR	DIRECTOR	CHIEF EDITOR
2000	Aric David Parnes	Rajan Puri
2001	Sonia Chacko	Jarrod Wall
2002	Ray Walls	Ashish Jain
2003	Ciara McLaughin	Heather Church
2004	Brenda Rice	Des McMahon
2005	Rebecca O'Rourke	Ciaran McMullan
2006	Rachael Liu	Peter Lonergan
2007	Michael Ednie	Jared Butler / J. David Ryan

Dublin University Biological Society
133rd Session

Activities Include:

Freshers' Social Events
Booksale
Halloween Ball
Med Cup
Med Day
Eid Celebration
Christmas Pantomine
Christmas Trip
Community Outreach Programme
Inaugral Meeting
Med Ball
Consultant Debates
Final's Night
Graduation Ball

Get Involved - It's *YOUR* Medical Society!

TSMJ Wants Your Articles!

The TSMJ provides a unique opportunity for undergraduate students to receive publication credit prior to graduation. Although we are edited and produced by students from Trinity College, submissions from educational institutions, other than our own, are also extremely welcome. Our submission categories range from original research to ethics based essays.

BRIEF OVERVIEW OF OUR TIME COURSE

We normally open for submissions at the start of December and close at the end of January, although this can vary somewhat from year to year. This is followed by a brief editing period. During this time, successful submissions are chosen and feedback by an editorial team on alterations to the articles that are required to bring them to the standard for publication is given. Subsequently, the production team format the journal and a launch conference is generally held in May.

TIPS FROM THE EDITORIAL BOARD

During our time editing the ninth edition of the TSMJ, the editorial board have come across a wide variety of different submission styles. We have decided to include some tips for people that intend to submit to the TSMJ or any other medical or scientific journal in the future. It is the hope that these tips will help the novice writer succeed in becoming published.

Decide on a topic and stick to it: It is important that there is a common theme running through the article. A well-written short article about a defined subject is far superior and more likely to be published than to a long complicated article that digresses from the point midway through.

Read articles published in journals such as the New England Journal of Medicine or the British Medical Journal: The authors should allow themselves to become familiar with how experienced writers of science or medicine put articles together. In particular, concentrate on the type of article you intend to submit, for example a case report is written in a very different style to a review.

Learn the specific requirements of the journal: Every journal has a specific formula under which it expects to receive articles. Before submission, consult the journal's website in reference to the specific requirements of the journal e.g. the format of pictures, graphics, figure legends or the length of abstract allowed. An article that arrives well polished will have a greater chance of being published.

Don't be afraid to take a chance at writing an article: If a topic interests you that you would like to write about or if you have carried out some research that you would like to see published why not try your hand at writing it up. Supervisors of projects are usually very helpful in these situations so approach them to ask for advice if you happen to have access.

Further guidelines and information is available on our web page www.tcd.ie/tsmj
Please feel free to contact us with any questions at tsmj@tcd.ie.

Regards,

The TSMJ Committee 2008

TSMJ Scholarship Winners 2007

Congratulations to Catherine Graham and Andrew Dold who were awarded last year's TSMJ Scholarships. We would like to thank St. James's Medical Board and Adelaide Meath incorporating the National Children's Hospital Medical Board who sponsored the awards. They are awarded on the basis of extracurricular excellence.